THE HEALTH OF BUS DRIVERS
A STUDY IN LONDON TRANSPORT*

L. G. NORMAN
M.D., B.Sc. Lond., M.R.C.P., D.P.H.
CHIEF MEDICAL OFFICER, LONDON TRANSPORT EXECUTIVE

London Transport is the largest urban passenger transport undertaking in the world. The amalgamation of over a hundred different undertakings into one transport system in London was largely due to the genius and foresight of one man. It is a romantic story. Albert Stanley, later Lord Ashfield, emigrated to the United States as a small boy with his parents and by the age of 20 was manager of the Detroit Street Railway Company. He returned to London in 1907 and his ambition to unify London's transport system was realised by the formation of the London Passenger Transport Board in 1933. The board was replaced by the London Transport Executive in 1947 under nationalisation. At the end of 1957 there were over 87,000 staff on London Transport's payroll, of whom 20,250 were drivers on the roads of Greater London. Of these, 14,000 were drivers of diesel double-decked buses in the Central area, 3000 drove country buses and Green Line coaches, and 3250 drove trolleybuses. These men—for all drivers are men—drove 6153 Central buses, 1206 country buses, 355 Green Line coaches, and 1611 trolleybuses, over a total of 609 routes covering 8829 route miles; in 1956 they carried 3236 million passengers, an average of 8,865,000 on every day of the year.

The London Transport Medical Service deals only with members of the staff. Its work is divided into three sections:

1. In the *Medical Examinations Section* over 40,000 examinations are made annually. The purpose of medical examinations is to ensure so far as possible that an applicant or employee is fit and able to do his work without endangering his own health or safety or that of others. The safety of the travelling public is paramount in this respect. Applicants for employment in any capacity are medically examined and certified fit before they start work. In addition, examinations of employees are undertaken after long absences due to sickness—four weeks for those who work on vehicles and eight weeks for others—and on certain other occasions. Any employee may seek medical advice on any aspect of his health in relation to his work. Trained nurses deal with accidents and sickness at work for the 10,000 employees at larger repair works.

2. The *Environmental Hygiene Section* supervises environmental working conditions, to ensure as far as possible that no hazard to health arises to any member of the staff in the course of his work. Under this section are included such matters as heating, lighting, ventilation, avoidance of excessive noise—the "heat, light, and sound" of occupational health—control of chemical hazards, the planning of new buildings, and routine inspection visits to all premises. Particular attention is paid to the maintenance of a high standard of food hygiene in the 186 staff canteens operated by London Transport.

3. Under the *First Aid Section* some 2000 employees are trained to undertake the immediate treatment of cases of accident or sickness. They take this training voluntarily in their own time.

Every employee has his own family doctor under the National Health Service, and our medical service does not treat sick or injured members of the staff, except in emergency. There are 10 full-time medical officers who, among other duties, examine all applicants for driving and all employed drivers.

The Public Service Vehicles (Drivers' & Conductors' Licences) Regulations, 1934, require bus drivers to possess a valid ordinary driving licence (D.L.2) and to hold a public-service-vehicle (P.S.V.) driving licence. Before the P.S.V. licence is first issued the driver must be medically examined and a certificate given to the effect that, inter alia, he is not suffering from any disease or physical disability which is likely to cause his driving of a public-service vehicle to be a source of danger to the public. This certificate may be issued by any registered medical practitioner. The P.S.V. licence is renewed every three years, and in the Greater London area drivers are required to undergo a medical examination, with issue of a similar certificate, (*a*) at the licence renewal date nearest the ages of 50, 56, and 62; and (*b*) on attaining the age of 65 and annually thereafter.

The minimum age for drivers in London Transport is 24; a small number continue to be employed after the age of 65 and all retire by their 70th birthday.

In addition to the statutory medical examinations, London Transport regulations require drivers to be medically examined: †

(*a*) Before employment as driver.
(*b*) Before returning to work after absence due to sickness lasting more than twenty-eight days.
(*c*) Before returning to work after absence due to accident, whether on or off duty, lasting more than three days.
(*d*) After any sickness causing the driver to stop work during his shift.
(*e*) At any time at the request of the management (e.g., when there is increased frequency of accidents).
(*f*) When any driver suffers from vertigo, heart-disease, epilepsy, fainting, or tuberculosis, whether he is absent from duty or not.
(*g*) At the age of 65 and annually thereafter.

In addition, routine examinations of eyesight are undertaken at the ages of 50, 55, 58, 60, 62, 64, and 65, and annually thereafter.

Selection and Training of Drivers

The most important single measure for preventing accidents on the roads is the selection and training of drivers. Drivers of buses are carefully selected from those who apply for this work; no such careful selection can exist for drivers of private vehicles. Evidence of the value of the selection procedures adopted, and perhaps also of the skill of the professional driver compared with the amateur, is found in the accident-rates for different types of vehicles. Table I, derived from an investigation by Manning (1949), illustrates this. Only accidents resulting in death or injury to one or more persons have been included. The lowest rate is that for passenger-transport drivers.

The selection procedure for drivers in London Transport is as follows:

1. The applicant has to complete a record of his employment during the previous five years, and references covering the previous two years' employment are taken up. Of those accepted, about 44% are recruited from the grade of con-

* A lecture given at Harvard University School of Public Health, Oct. 10, 1957.

† As from Oct. 1, 1958, drivers will, in addition, be medically examined at the ages of 50, 56, and 62, with an examination of eyesight only at the age of 59.

TABLE I—PERSONAL-INJURY ACCIDENT-RATES FOR DIFFERENT TYPES OF VEHICLE

Type of vehicle	Vehicles involved in accidents per million vehicle-miles	Average no. of vehicle-miles travelled per accident
Buses	6·5	154,000
Commercial vehicles	7·0	143,000
Private cars	7·5	133,000
Pedal cycles	8·6	116,000
Motor cycles	23·4	43,000
All vehicles	8·5	117,500

ductor, some of whom may never have driven a vehicle before. The remainder are recruited from outside the service, mainly from men who are experienced commercial-vehicle drivers.

2. The applicant is interviewed by a trained and experienced interviewer, who assesses his personality.

3. A test drive (aptitude test) is undertaken, the applicant's suitability for training as a driver being assessed by an experienced instructor.

4. About half those who apply pass the selection interview. They are then sent for eyesight and medical examination. The eyesight standard required is:

(*a*) Distant vision 6/9 6/12 without glasses.
(*b*) If the uncorrected vision is worse than 6/9 6/12, but not worse than 6/12 6/24, the applicant is accepted, provided he obtains glasses which correct the vision to at least 6/9 6/12 and that these glasses are always worn when he is on duty.
(*c*) Ability to pass the colour-vision test.
(*d*) The visual fields, as ascertained by hand confrontation, or similar test, must be normal.
(*e*) There must be no obvious strabismus.
(*f*) There must be no ocular disease such as cataract, detached retina, retinitis, or active choroiditis.

Tests of simultaneous binocular vision, stereoscopic depth perception, vertical and lateral ocular muscle balance, and dark adaptation are not routinely undertaken. The high eyesight standard on entry allows a considerable margin for deterioration with age. Drivers already in the service are required to attain a lower eyesight standard, which is regarded as the lowest consistent with safe driving. This is:

(*a*) Distant vision 6/12 6/24 without glasses. (Where the visual standard can be improved by glasses, the driver is advised accordingly.)
(*b*) If the uncorrected vision is worse than 6/12 6/24, but not worse than 6/60 6/60, the driver must obtain glasses and is acceptable if the corrected vision is not worse than 6/9 6/36 and these glasses are always worn when he is on duty.
(*c*) The visual fields as ascertained by hand confrontation, or similar test, must be normal.
(*d*) There must be no ocular disease such as cataract, detached retina, retinitis, or active choroiditis.

Any driver whose distant visual acuity is found to have deteriorated is referred for examination by an ophthalmic surgeon. The test of visual fields is particularly important for older drivers, for the incidence of glaucoma increases with age.

Fig 1—A driver.

The medical examination of applicants for driving consists of a general clinical examination, including blood-pressure measurement and urine tests for albumin and sugar. It does not include, as a routine, electrocardiograms or chest radiographs, such special tests being undertaken only if clinically indicated. The hearing must be normal to a conversational and whispered voice test.

Of those who are medically examined, about 20% are rejected. Half the rejections are due to failure to reach the eyesight standard and the other half to various pathological conditions which would render the applicant unsafe or inefficient as a driver.

Applied psychological tests are not used for the selection of drivers, nor is the "reaction time" test. Fig. 1 is a photograph of a driver; he is relaxed and completely at his ease. He is not taught to be tensed and ready for instant depression of the pedals, as in the reaction-time test. On the contrary, he is taught relaxation and to drive by anticipation, that is, to look well ahead and so avoid getting into the accident situation. Together with the allowance of full play for the other road users' errors, this preventive technique is the basis of safe driving.

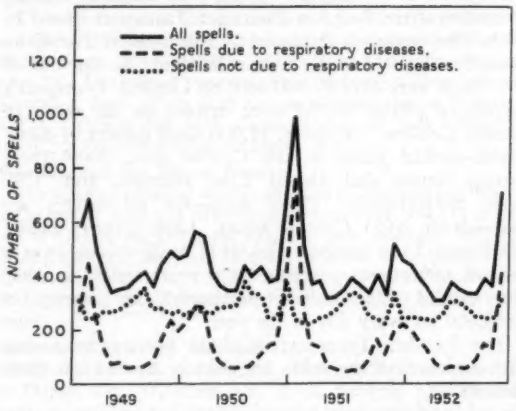


Fig. 2—Sickness spells of Central Bus drivers lasting 4 days or more commencing in each 4-weekly period 1949-52.

An adequate period of training by highly skilled instructors is a most important factor in accident prevention. In London Transport the average time taken in training a driver who has never driven before is 50 hours at the wheel, spread over at least four weeks; experienced drivers may require almost as long to "unlearn" some of their faults, while others learn quickly. Periodic tests are given during the period of training, and about 20% of those who enter training fail to complete the course; the process of selection is thus continued during the training period and the standard required becomes progressively higher. At the end of his training the potential driver is given experience of skidding on a special skid track. Finally, he has to pass a stringent test in which he drives a bus for an hour or more through the London streets.

Only one out of every four applicants to drive actually passes all the examinations and tests and obtains his licence.

The Sickness Absence of Drivers

It is remarkable that, with all our knowledge of the causation and cure of disease, we have little better idea of the nature of health than had the ancient Greeks over two thousand years ago. We cannot measure health,

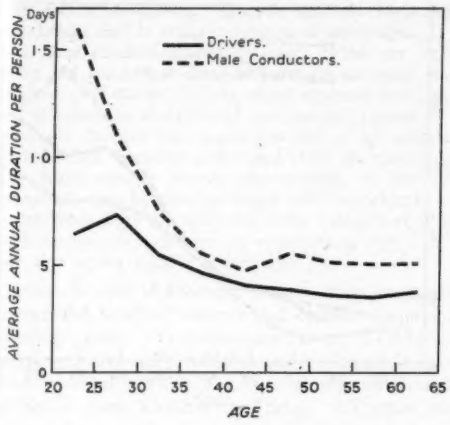


Fig. 3—Absences of 1, 2, or 3 days. 1949-52.

either in the individual or in the group. Nor have we any very precise measurements of sickness. What we can measure with considerable accuracy is the amount of absence from work caused by sickness, both of individuals and of groups. Such measurements provide the best known method of studying the health of groups. There is an " iceberg phenomenon " here; what is measured is morbidity that is severe enough to cause absence, but there is a great amount of minor morbidity that is under the surface and does not cause absence from work. Total morbidity can be measured only by survey technqiues.

There is no uniform threshold level of the severity of an illness that is sufficient to cause absence from work; some individuals take absence very easily, others only if the illness is more severe. An accurate measurement of group sickness-absence level will, however, be obtained if the group is large enough. The duration of absence caused by any one diagnosis is likely to be widely distributed. For certain diagnoses such as acute perforated peptic ulcer, it may be safely assumed that all those affected will be absent from work.

In London Transport a particular study has been made of the absence from work, due to sickness, of several large occupational groups of employees. One of the groups studied comprised about 14,000 diesel-bus drivers employed at the Central bus garages (*Health in Industry* 1956).

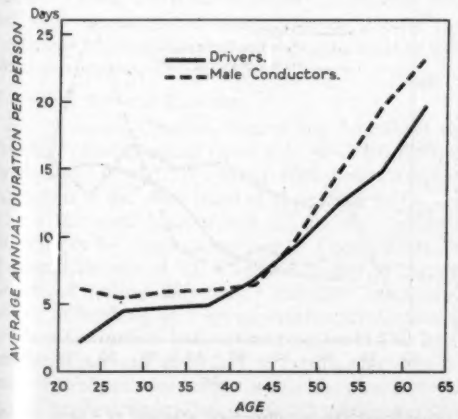


Fig. 4—Absences of 4 days or more. 1949-52.

Fig. 2 shows, for drivers, the total number of spells (that is, occurrences) of sickness absence lasting for four days or more, from the beginning of 1949 to the end of 1952. It also shows these spells divided into respiratory and non-respiratory causative groups, and demonstrates that the seasonal variation is due almost entirely to the respiratory diseases. It is often overlooked that a single year is too short a period of observation. Thus there was a mild influenza epidemic in the winter of 1950–51, and a study based only on the period April, 1950, to March, 1951, would have been atypical and misleading. Studies of sickness absence must therefore be based on at least three years' experience.

There is a great difference between the characteristics of short sickness absences and those of the longer absences.

Fig. 3 shows, for drivers and male conductors, the average annual duration per person of absences of one, two, and three days. Both drivers and conductors have more short absences at the younger ages. This may be due to the greater responsibilities—and the greater sense of responsibility—of the older men; or to a larger amount of short-term infectious illness in younger men; or to the fact that younger men recover more quickly from a condition of specific severity; or to other factors unknown.

Medical certificates are not usually required for these short-term absences, and undoubtedly many are due to social and economic factors and not to sickness at all. In studying sickness absence, the short three-day absences must therefore be separated from the absences of four days and over for which a medical certificate is required. For statistical purposes, in order to ensure homogeneity, the recording of long-term absences is terminated at six months (182 days). The great majority of the longer absences are undoubtedly due to genuine sickness.

The conductors form a useful control group for the drivers.

The comparison is fair. There are large enough numbers in each group to satisfy statistical requirements, for there were about 14,000 drivers and 12,000 male conductors included in this study; the observations are divided into five-year age-groups and are therefore age-standardised; the social and residential circumstances of drivers and conductors are similar; their pay is nearly the same (the maximum rate of pay of a driver is about 5*s*. a week more than that of a conductor); and such factors as the accuracy of medical certification by the men's own doctors apply equally to the two groups.

Differences between drivers and conductors arise (1) because of the nature of their work; (2) because transfer from conductor to driver is a promotion; (3) because a man may prefer either driving or conducting; (4) because selection procedure may push him in one or other direction. But (5) even at the age of 25, before the actual occupation can have had any effect (drivers are not recruited below the age of 24), there is a somatotype difference between drivers and conductors which may be accompanied by genetic and personality differences which may in turn affect sickness absence (Morris et al. 1956).

Any difference in the sickness absence of drivers and conductors which results from occupation would be expected to increase with length of service and therefore to be greater in the higher age-groups. In fig. 4, which gives the average annual duration per person of absences of four days' duration or more, the effect of age is immediately apparent. For both drivers and conductors the amount of absence is about four times as great at the age of 60 as it is at 30. It is obviously useless to study the sickness absence of a group without taking account of its age distribution. The total amount of sickness absence—i.e, short and long absences added together—

ranges from 5·228 days per driver at the age of 25–29, to 20·054 days per driver at 60–64. These levels are not high in comparison with other occupational groups, and they indicate that drivers are a healthy group of men who do not suffer excessively from any particular occupational disease.

Fig. 4 reveals a difference between the absences of drivers and conductors. Except in the age-group 40–44, conductors have more sickness absence than drivers, and this difference becomes progressively greater as age—and therefore length of service—increases beyond 45. This may be due to (1) genotype and selective factors, (2) the effects of the different occupations, or (3) the fact that drivers can remain at work when suffering from a degree of illness which would require conductors to be absent—driving is largely a sedentary occupation, whereas a conductor must be exceedingly mobile. If this last factor is significant, we should expect the amount of absence due to bronchitis, for example, to be greater in conductors than drivers, for conducting requires more physical exertion than driving. Fig. 5 shows that, except in the age-group 40–44, conductors do in fact experience more

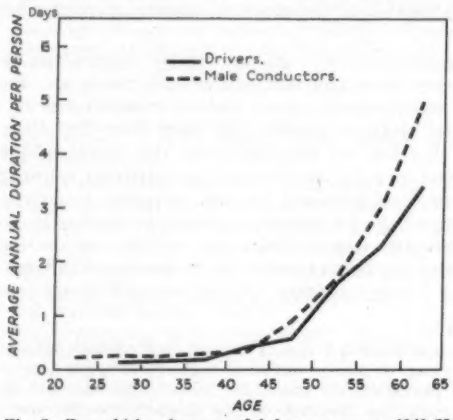


Fig. 5—Bronchitis: absences of 4 days or more. 1949-52.

absence due to bronchitis than drivers, and that this difference increases progressively after the age of 45.

In fig. 5 and in succeeding charts the diagnoses are those included in the 3-figure code of the International Statistical Classification of Diseases and Injuries adopted by the World Health Organisation in 1948. Bronchitis, for example, includes "acute bronchitis", "chronic bronchitis" and "bronchitis, unspecified", which are nos. 500–502 of this code. An increase in absence caused by bronchitis after the age of 45 occurs in all male groups of staff studied and to a lesser extent in female groups.

Bronchitis causes 3·7% of the sickness absence of London bus drivers at the age of 30–34 and no less than 17·3% at 60–64. Bronchitis, the English disease, is a major national health problem: it causes industry the loss of about 40 million man-days a year.

Gastroduodenal Disorders

It has often been suggested that transport workers have an excess of gastric disorders, but Avery Jones and Doll (1951) found peptic ulceration no more common in the drivers and conductors of passenger-transport vehicles than in industrial workers generally. In the present study diseases of the stomach and duodenum which are included in the code numbers 540–545 inclusive and 784 of the International Statistical Classification have been grouped

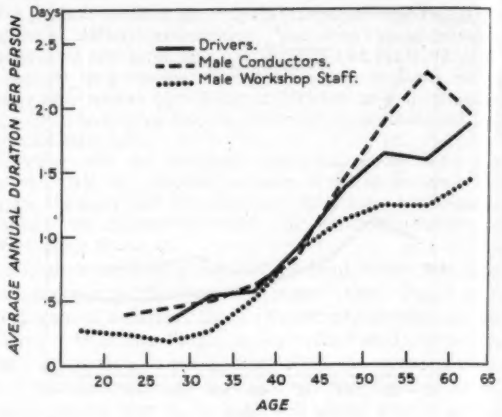


Fig. 6—Diseases of stomach and duodenum: absences of 4 days or more. 1949-52.

together. Fig. 6 shows the average annual duration per person of absences due to these conditions for three groups of employees—drivers, male conductors, and male workshop staff. Absence due to diseases of the stomach and duodenum is seen to be higher among drivers and conductors than among workshop staff, except in the age-group 40–44.

What is the explanation of this?

First, there is no doubt that the difference is real. The smallest of the three groups (workshop staff) covers over 15,000 man-years of exposed-to-risk; the other two groups cover about 50,000 man-years each. The numbers of observations in each group are therefore sufficient to satisfy the most sceptical statistician.

The three groups are socially comparable and their average earnings are not widely different; they work for the same employer under broadly similar conditions of employment. All absences are certified by medical practitioners and any variations or inaccuracies in certification should apply equally to the three groups. The doctrine has been taught in medical schools that peptic ulceration is more prevalent in men who drive others, who drive themselves, and who drive vehicles; it might therefore be that drivers, and perhaps conductors, are certified as suffering from gastric illnesses more often than their workshop colleagues. Such an excess of certification, however, would be expected to apply at all age-groups, whereas the excess in drivers and conductors in fact disappears

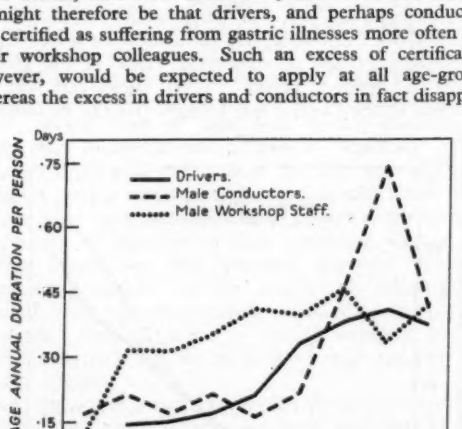


Fig. 7—Functional nervous disorders: absences of 4 days or more. 1949-52.

in the middle age-groups. It seems unlikely that a real excess in workshop staff is being concealed at these ages.

The fact remains, therefore, that, below the age of 35, drivers and conductors have about twice as much absence as workshop staff due to diseases of the stomach and duodenum; from 45 onwards, drivers and conductors experience increasingly more absence than workshop staff as age advances, but the difference between them and their workshop brethren never again reaches double the amount of absence. One explanation may be that workshop staff are able to continue at work when they are suffering from a degree of illness that would incapacitate drivers or conductors, but this should apply also to the middle age-groups.

There is one difference, which may be significant, between the work of drivers and conductors and that of workshop staff. The busmen work a rotating-shift system, working early, middle, and late turns in successive weeks, whereas workshop staff work regular daytime factory hours from Monday to Friday. All other variables

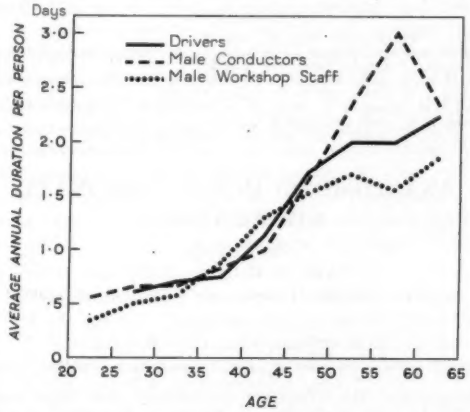


Fig. 8—Functional nervous disorders plus diseases of stomach and duodenum: absences of 4 days or more. 1949-52.

are as nearly as possible comparable between the two groups and it may be that there is here a demonstration of the effects of shift working on absence due to gastric and duodenal conditions. It still remains to be explained, however, why the difference between the occupational groups concerned disappears at around the age of 35. Since actual peptic ulceration is no commoner in drivers and conductors than in other workers (Avery Jones and Doll 1951), the difference between busmen and workshop staff now demonstrated must be even greater in other conditions in the gastroduodenal group, such as the functional dyspepsias.

Functional Nervous Disorders

Fig. 7 shows absences due to the functional nervous disorders (International Code nos. 300–318) for the same three groups of staff. Workshop staff start at a higher level but maintain the even tenor of their ways to the end; for drivers the road leads uphill all the way (albeit rather gently); but for conductors there is a remarkable increase at around the age of 50. Can this be due to the strain of the job, of dealing daily with " difficult " members of the public, of working at a speed which must be maintained by the older men as well as the younger? The decline in functional nervous disorders of conductors over 60 may mean that those who cannot stand the pace have left the job. Why do absences due to functional nervous disorders in workshop (factory) staff increase so little with age?

In fig. 8 are added together the average annual duration per person of absences caused by functional nervous disorders and diseases of the stomach and duodenum; both disease groups consist mainly of psychosomatic illnesses. The same three groups of staff experience roughly the same amount of absence until the age of 50 when they diverge considerably; at the ages of 55–59 conductors experience about twice as much absence due to these illnesses as workshop staff, with drivers occupying an intermediate position. About a third of this excess in conductors is due to the functional nervous disorders and two-thirds to diseases of the stomach and duodenum.

Comment

These studies demonstrate that the health of London bus drivers, as measured by their sickness absence, differs from that of other workers in the industry and even from that of their colleagues, the conductors. The reasons for these well-marked occupational differences are not obvious and are probably multiple.

Loss of Consciousness While Driving

Loss of consciousness in a driver who is actually driving a vehicle is a dramatic but fortunately uncommon event. The conditions which may cause it are:

Falling asleep.
Epilepsy in most of its forms.
Laryngeal vertigo.
Coronary-artery disease.
Aortic valvular disease, auricular fibrillation, cerebral and pulmonary embolism.
Simple fainting attacks, syncope, cerebral anæmia, hypotension.
Cerebral accidents.
Hypoglycæmia.

Hypnotic, hypotensive, and certain anti-histaminic drugs may reduce the level of consciousness to the point where it is lost. Hypertension, Ménière's syndrome, labyrinthitis, and chronic suppurative otitis media may cause attacks of giddiness without actual loss of consciousness.

Three points of particular importance may be noted:

(*a*) Idiopathic epilepsy may occur for the first time in middle life. Thus Nattrass (1949) and Berlin (1953) have reported series of cases of epilepsy occurring in men over 40 in which no evidence was found of any progressive brain lesion.

TABLE II—LOSS OF CONSCIOUSNESS WHILE DRIVING VEHICLES (EXCLUDING CASES OF CORONARY THROMBOSIS)

Case	Diagnosis	Any collision or damage?	Had driver enough warning of attack to stop vehicle?	Remarks
1	Lobar pneumonia	No	—	Vehicle had stopped
2	Unknown. ? petit-mal	Yes	No	Drove into roundabout; gave incorrect history of burst tyre
3	Fibrositis (?)	No	Yes	—
4	Unknown. ? petit-mal	Yes	No	—
5	(1) Epilepsy (2) Spontaneous hypoglycæmia	No	—	Vehicle had stopped
6	Laryngeal vertigo due to whooping cough	Yes	No	—
7	Laryngeal vertigo	Yes	No	—
8	Muscular cramp with reflex hypotension	Yes	No	—
9	Hypertensive encephalopathy	No	No	—
10	Epilepsy	Yes	No	—
11	Epilepsy? (age 26)	Yes	No	Provisional diagnosis
12	Laryngeal vertigo	Yes	No	—
13	Vasovagal syncope?	Yes	No	—
14	Subarachnoid haemorrhage	Yes	No	—
15	Vasovagal syncope	Yes	No	—
16	Epilepsy (age 45)	Yes	No	Normal E.E.G.
17	Epilepsy?	Yes	No	Provisional diagnosis
18	Vasovagal syncope	Yes	No	—

TABLE III—LOSS OF CONSCIOUSNESS, DUE TO CORONARY THROMBOSIS, WHILE DRIVING VEHICLES

Case	Any collision or damage?	Had driver enough warning of attack to stop vehicle?	Remarks
19	No	—	Vehicle had stopped
20	No	No	Vehicle was moving slowly and was stopped by conductor
21	No	Yes	—
22	No	Yes	—
23	Slight	No	Vehicle bumped gently into road island and stopped
24	Minor	No	Minor collision with van
25	No	Yes	Onset preceded by exertion
26	No	No	—
27	Yes	No	—
28	No	Yes	—

(*b*) It is well known that the brain is a common site for secondary growths from carcinoma of the lung and bronchus. The first manifestation of such secondaries may be an epileptiform loss of consciousness. I have now found 3 cases of carcinoma of the bronchus in which the first sign of any illness was the epileptiform attack. Public-transport drivers who have been treated for carcinoma of the bronchus should not be allowed to resume driving.

(*c*) Laryngeal vertigo (cough syncope) is a common condition. Most drivers will report it, but the physician is well advised to question specifically for this condition in those of his patients who are drivers.

Among about 20,000 drivers over a period of eleven years—say 220,000 driver-years—28 cases have occurred in which they lost consciousness while actually driving. Details of some of these cases have been published elsewhere (Norman 1954). The cases fall into two main groups—18 cases due to various medical conditions, and 10 cases due to coronary thrombosis. Table II summarises the former.

In 2 cases the vehicle was already stationary when the driver had his attack. In all but 1 of the remaining 16, the driver did not have enough warning to stop his vehicle.

In 2 cases there were fatal accidents; damage and personal injuries were minor in the remainder. Case 10 (epilepsy) resulted in the death of a motorcyclist and in case 18 8 pedestrians lost their lives when the vehicle mounted a crowded pavement. The driver in this case was aged 62. He was fully investigated and the conclusion was definitely reached that he had had a simple vasovagal syncopal attack. It is remarkable that such attacks are so rare.

Table III summarises the losses of consciousness due to coronary thrombosis while drivers were actually driving. In most cases the driver died suddenly.

In 4 cases the driver had sufficient warning of the attack to stop the vehicle, but in 5 cases he had not, and in 3 of these there was an accident. In the remaining case the vehicle had stopped before the onset. The conclusion is inescapable that public-transport drivers who suffer from coronary-artery disease should cease to drive. There is, of course, at present no satisfactory way of detecting the imminence of such attacks in drivers who have no previous history of the disease.

London Transport drivers who suffer from recognisable conditions likely to cause loss of consciousness are taken off their driving duties after one of their periodic medical examinations. Tables II and III probably represent the inescapable minimum of incidents arising from such illness.

Summary

An account is given of the statutory and periodic medical examinations of London Transport bus and trolleybus drivers. The selection and training of drivers are described. The visual and medical standards required for employment as driver are given. The sickness absence of drivers does not reveal any particular occupational disease, but there are differences in the pattern of sickness between drivers and conductors, and between drivers and other occupational groups.

The medical conditions which may cause a driver to lose consciousness while driving are listed, and a summary is given of 28 cases in which such loss of consciousness occurred. 10 of these cases were due to coronary thrombosis and 18 to other medical conditions. In 4 of the coronary-thrombosis cases the driver had enough warning to stop his vehicle, but in 5 he did not and in 3 of these an accident resulted. Public-transport drivers who suffer from coronary-artery disease should no longer drive.

I am grateful to many colleagues in London Transport for their help in the preparation of this paper.

REFERENCES

Berlin, L. (1953) *J. Amer. med. Ass.* **153**, 794.
Health in Industry (1956); A Contribution to the Study of Sickness Absence: London Transport Executive. London
Jones, F. A., Doll, R. (1951) *Spec. Rep. Ser. med. Res. Coun., Lond.* no. 276.
Manning, J. R. (1949) *Rds & Rd. Constr.* **27**, 290.
Morris, J. N., Heady, J. A., Raffle, P. A. B. (1956) *Lancet*, 1956, ii, 569.
Nattrass, F. J. (1949) *Brit. med. J.* i, 43.
Norman, L. G. (1954) *Trans. Ass. indust. Med. Offrs*, **4**, 3.

ANASTOMOSIS IN THE CORONARY CIRCULATION

W. LAURIE
D.S.O., M.D. Glasg., T.D.D.
DEPUTY PROVINCIAL PATHOLOGIST, NATAL, SOUTH AFRICA

J. D. WOODS
M.B. W'srand, F.R.F.P.S., M.R.C.P.
HEAD OF THE DEPARTMENT OF MEDICINE, EDENDALE HOSPITAL, NATAL

ALTHOUGH the coronary circulation has been under investigation for many centuries there is still no definite agreement on the findings. Gregg (1950) points out that "in no field of circulation have our views changed more frequently than in the interpretation of the coronary circulation". The earliest view was that significant anastomoses exist between the two sides of the heart; but opinion oscillated, and in 1881 Cohnheim and Schulthess von Rechberg (cited by Gross 1921), from observations in dogs, concluded that the coronary supply is by true end-arteries; this view was widely accepted and still is accepted by some workers.

With the introduction of roentgenology more exact techniques of investigation became available, and this aid became much used in studies on the coronary system. Gross (1921), in his review of previous work and in his summary of his own work, concluded that "the heart is perhaps the richest organ in the body as regards capillary and pre-capillary anastomoses between the branches of the same coronary artery as well as between branches of both arteries". Gross considered the capillary anastomosis to be the more important, and he claimed that the degree of anastomosis increased pari passu with the age of the patient: "the older the patient the more free and patent are the anastomoses". He further claimed that where such anastomoses exist they are fully occupied and functioning and are not available to act as compensatory agents should the need arise.

The next advance came from Schlesinger (1938), who utilised the coronary-injection techniques of previous workers and introduced a method of so opening the heart

that the skiagram gives a picture with the one coronary system separated from the other. In a series of important papers Schlesinger and others (Schlesinger 1938, 1940, Blumgart et al. 1940, 1941) came to three conclusions:

1. In the heart, functionally important anastomoses develop only in response to disease—i.e., they develop "where and when needed". Age alone plays no part in the development of such anastomoses. Where there is no disease, there are no anastomoses even in the senile heart.

2. Capillary communications regularly exist between the right and the left coronary arteries in normal hearts, but these fine communications are of questionable functional significance. The survival of the affected individual, and his relative comfort during survival, depend upon the development of anastomoses of arteriole size (40 μ and greater).

3. Functionally speaking, the coronary arteries in normal hearts, even senile hearts, are true Conheim end-arteries without anastomotic connections.

In his original paper Schlesinger (1938) based his conclusions on a series of fifteen normal and twenty-three abnormal hearts; he excluded all patients under fifty years of age because, he claimed, previous workers had shown that anastomoses are unlikely to be fully established below that age.

Schlesinger et al. make it clear that it is only ischæmic heart-disease that is likely to result in the formation of anastomoses; "anastomoses measuring 40 μ or more in diameter between the right and the left coronary artery do not exist in the absence of partial or complete occlusion of these arteries". The authors list such ischæmic diseases:

1. Diseases decreasing the supply of blood.
   (*a*) Mechanical obstruction to blood-flow, the most important of which is atherosclerosis of the coronary arteries but which also include conditions affecting the ostia of the arteries of the heart.
   (*b*) Pulmonary infection or œdema causing anoxæmia; or low blood-pressure.
2. Diseases increasing the work of the heart—e.g., hypertension, valvular disease, anæmia.

It would follow that conditions affecting the myocardium directly (e.g., diphtheria) would be unlikely to cause production of anastomoses.

The problem of the coronary-artery anastomosis is not an academic one only. Blumgart et al. (1940) state that "anastomotic circulation to an extraordinary degree may obviate any serious consequences of complete coronary artery occlusion", and they cite cases in which all three main coronary branches had been occluded but the patients lived fairly comfortable lives because of adequate coronary anastomoses. Bourne (1957) cites similar case-records.

The most important source of such anastomotic supplies is between branches of the same coronary artery and between the two main coronary arteries themselves, especially in the epicardial field (Gregg 1950). Schlesinger (1938) claimed that the left coronary artery was the more important source of anastomotic supply, although the right coronary artery is the major vessel in the majority of people.

The methods of investigation used by Schlesinger and his coworkers (see below) are now widely utilised, and we adopted them as one approach in a study of coronary heart-disease in the Bantu. By these methods, and subsequently by simpler methods, we obtained results so different from those reported by Schlesinger and others that we consider the question should be reopened. This preliminary report is based on our findings to date.

Methods

Much of the difference of opinion on the work dealing with coronary anastomosis has probably arisen due to differences in techniques. It is necessary to study the techniques in detail.

Reference has been made to the opinion that the anastomoses which will maintain life in an ischæmic heart are those of 40 μ and upwards—i.e., arteriole size. Any method of investigation of the anastomotic circulation should therefore be carried out, using particulate matter too large to pass the capillary filter, but small enough to enter the arterioles; and this particulate matter must be suspended in a medium so viscous itself as to be unlikely to pass through the capillaries. Gross (1921) used barium sulphate suspended in gelatin, a mixture with a viscosity of about fifteen times that of heparinised blood. Schlesinger (1938) used lead-phosphate/agar, which is three times more viscid than heparinised blood; he claimed that, under the pressures he used, this mass will penetrate all vessels of diameter 40 μ or more. Vessels of this size fall into the category of arterioles; according to Prinzmetal et al. (1947) the calibre of capillaries in man averages 8 μ only.

Schlesinger (1938) used a red injection mass for one artery and a blue mass for the other. After perfusing the arteries with physiological saline solution he introduced these masses simultaneously at first, perfusing both arteries at a pressure of 150 mm. Hg (this has been shown by Gregg [1950] to be a physiological pressure). The perfusion pressure on one side was then dropped to zero, the other being maintained at 150 mm Hg. After a short time he reversed the pressures on the two sides. A purple staining was thought to indicate anastomosis.

Preliminary studies on thirty-five hearts by this method indicated disadvantages: recognition of colour changes was not easy, and it was difficult to dissect and recognise the colour in vessels smaller than 800 μ. It was doubtful, moreover, whether the two viscid suspensions always mixed intimately at the low pressures prevailing in the small vessels. Accordingly a simpler technique was adopted in which only one vessel was perfused with a radio-opaque mass, with a cannula tied in the ostium of the other artery to prevent back leakage. Any filler material found on the other side of the heart could only have come from the perfused artery. This simple technique has been widely criticised; for example, Schlesinger terms it "crude". Such criticism, however, is not justified; in fact the see-saw method of Schlesinger is simply perfusion from one side only at one time.

In his original work Schlesinger (1938) used lead phosphate 8% suspended in 0·75% agar: as stated above, he claimed that this mass is three times more viscid than heparinised blood. Gelatin gives a much more viscid suspending medium than does agar (Gross 1921), and accordingly to make conditions as stringent as possible we used the lead phosphate of Schlesinger but suspended it in gelatin. The radio-opaque mass was prepared as follows:

Solution A.—Pure lead acetate (e.g., 'Analar') 60·0 g., distilled water 172·0 ml., filter.

Solution B.—Disodium phosphate (anhydrous) 24 g., distilled water 190 ml.

In a beaker add 100 ml. solution A and with constant stirring add 70 ml. of solution B. Now add 1 ml. of phenol-red indicator and add 40% sodium hydroxide until a faint permanent pink colour is obtained. The solution is now neutral. Add water to 200 ml., then add 18 g. of gelatin and heat until the gelatin is in solution, this giving a suspending medium of 9% gelatin.

The viscosity of this radio-opaque mass compared with heparinised blood was determined using a locally made viscosimeter of a design suggested by Prof. J. A. V. Fairbrother of the Department of Physics of the University of Natal. Different batches of the mass differed slightly one from the other as regards relative viscosity, but the average values suggested that the gelatin mass was about seven times more viscid than heparinised blood.

The particle size of the lead phosphate was estimated by Baird and Tatlock sintered glass filters and by microscopy of the perfused

hearts. Using a Baird and Tatlock grade-4 filter (porosity 5–15 μ) with a vacuum of 300 mm. Hg, none of the material under test passed through this filter; as the human capillary averages 8 μ the particles of the suspension used by us therefore would not pass the capillary barrier in the heart. Using the same technique and a grade-3 filter (porosity 15–40 μ) with the same vacuum only a trace of lead phosphate was found in the filtrate. This was confirmed by the microscopic examination of perfused hearts; it was found that in these hearts the smallest vessel to show contained perfusion material measured 35 μ in diameter. It is suggested therefore that in the suspensions used in this work the smallest particle measures not less than 35 μ; probably in the actual work of perfusing the hearts the particles passing through were much bigger owing to the speed of aggregation and the difficulty in maintaining uniform mixing of the suspension.

With the exception of the differences in the two suspending media and the difference in perfusing one instead of the two ostia of the coronary arteries, all our technique conformed to that of Schlesinger—namely, all perfusion was carried out with the heart immersed in saline solution at 45°C. First saline solution then the radio-opaque mass was introduced into one coronary ostium at a pressure of 150 mm. Hg; the perfusion of the radio-opaque mass continued for twenty minutes, then

TABLE I—FINDINGS IN 87 NORMAL PERFUSED HEARTS

Age-group (yr.)	Degree of anastomosis					Totals
	Nil	Quarter	Half	Three-quarters	Complete	
Under 1/12	7	—	—	—	—	7
1/12 to 23/12	16	5	—	2	2	25
2–4 ..	10	3	—	1	—	14
5–14 ..	1	—	—	1	1	3
15–24 ..	—	—	1	2	1	4
25–34 ..	—	1	2	1	—	4
35–44 ..	—	2	2	2	2	8
45–54 ..	3	1	1	1	4	10
55–64 ..	1	—	2	4	1	8
65–74 ..	1	—	—	2	—	3
75+ ..	—	—	—	—	1	1
Totals ..	39	12	8	16	12	87

still under pressure on one coronary artery the heart was immersed in iced physiological saline solution until the intra-arterial mass had hardened; the heart was then "unrolled" by the dissection technique of Schlesinger (1938) and a skiagram taken of the coronary circulation. Thereafter each coronary artery and major branches were dissected as far as possible, and finally sections of the heart and its major vessels were examined microscopically.

Throughout this series all the work except histopathology was carried out by one or other of the two authors. On many occasions normal and abnormal hearts injected at the same time showed clear differences in degrees of anastomoses found. This excludes the possibility that differences in findings of anastomoses in perfused normal and abnormal hearts were due to differences in technique or in the mass perfused.

Material

Our material is that described previously (Laurie and Woods 1958).

This hospital is in a native reserve, only 15% of the patients coming from the neighbouring urban areas. It is not a teaching hospital, and there is no selection either in the admitting of patients or in the carrying out of necropsies. A postmortem examination is made on about two of every three patients who die in the hospital.

From the time of our beginning the modification in technique—i.e., from the time of our perfusing only from one artery—there was no selection in the choice of hearts to be perfused. We perfused every heart obtained at routine consecutive necropsies; the series therefor includes both sexes and all ages from an 85-year-old adult to newborn premature children with hearts weighing only about 8 g. All the necropsy material was from Bantu and was drawn from all clinical sections of the hospital—medical, surgical, gynæcological, obstetric, and pædiatric. All the postmortem examinations were carried out by one of the two authors.

TABLE II—FINDINGS IN 63 DISEASED PERFUSED HEARTS

Age-group (yr.)	Degree of anastomosis*					Totals
	Nil	Quarter	Half	Three-quarters	Complete	
Under 15	(10)	(1)		(1)	(1)	(13)
15–24	2		(1)		(1)	2+ (2)
25–34			1+(1)			1+ (1)
35–44	7+ (1)		1		2	10+ (1)
45–54	6+ (1)	3+(1)	1		2+(1)	12+ (3)
55–64	10	1			1	12
65–74	2	1			1	4
75+	1		1			2
Totals	28+(12)	5+(2)	4+(2)	0+(1)	6+(3)	43+(20)

* Figures not in parentheses = ischæmic heart-disease. Figures in parentheses = non-ischæmic heart-disease.

Results

To date we have injected 200 hearts but have omitted from this review a total of 50 hearts as unsuitable for the study of anastomosis. These comprised 35 hearts injected by Schlesinger's technique and 15 others showing technical faults.

The first necessary division of findings is into "findings in normal hearts" and "findings in diseased hearts". No heart was classified as normal if any lesion was found at necropsy or in subsequent microscopic examination of heart sections.

In both normal and diseased hearts it is necessary to give a rough quantitative estimate of the degree of anastomosis present. In the tables I and II we have graded the degrees of anastomosis as "nil", "a quarter", "half", "three-quarters", and "complete". This grading is by comparison of the anastomosis under review with a picture of a well-filled coronary tree of the same side—i.e., a coronary tree perfused from its own ostium. Where the anastomosis is marked—three-quarters or more—this degree of anastomosis may go far towards

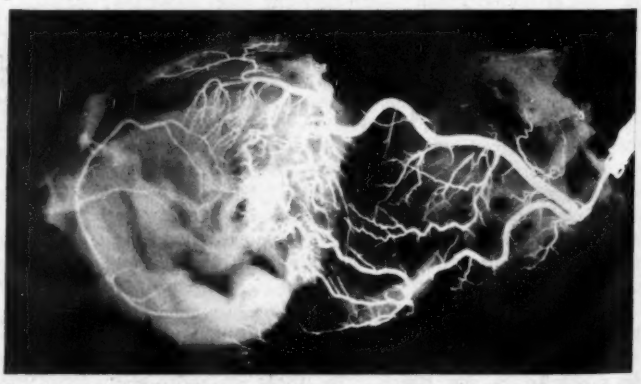


Fig. 1—Heart showing left ventricle supported only by anastomotic supply from two branches of abnormal right coronary artery; there was no left coronary orifice in this heart.

meeting the needs of the affected area of the myocardium in a cardiac emergency. The importance of the lesser degrees of anastomoses—i.e., our "half" and less—would have been hard to assess had it not been that early in this investigation we found one of the hearts obtained at necropsy showed only a right coronary ostium; both by skiagram following perfusion and from the resultant dissection of the coronary tree it was found that, in addition to a right coronary artery of normal distribution, a second large vessel branched off from the main stem 1 mm. from the right ostium and followed a course corresponding to a mirror image of the course of a left descending coronary branch in the normal heart. The whole of the left ventricle was fed by an anastomosis between the two main branches of the right coronary artery. In the skiagram (fig. 1) the degree of anastomosis present in the left ventricle would be classified by us as half. This heart came from a Bantu female who had died of a phthisic hæmoptysis; before that hæmoptysis the patient had led a normal life; she was married with two children. Here we have an example of a patient able to live a full life on an anastomosis classed as half.

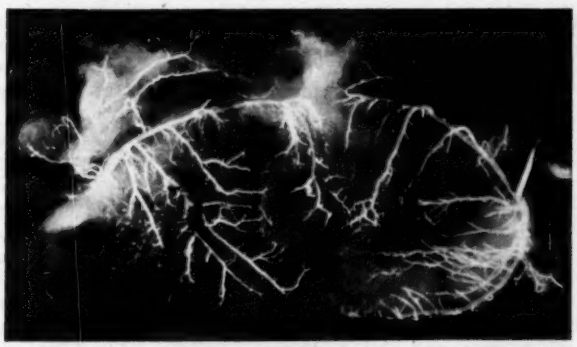


Fig. 3—Heart from healthy infant aged 9 months, showing complete anastomosis to one side from perfused material in other coronary artery.

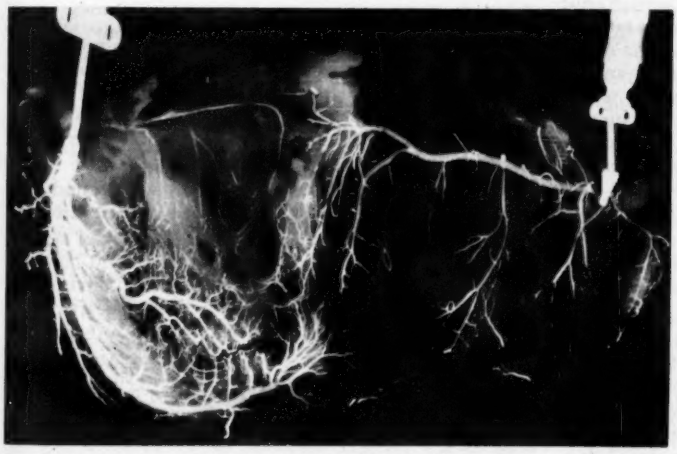


Fig. 2—Normal heart perfused only into left descending branch of left coronary artery, and showing substantial anastomoses both into left circumflex branch on same side and into right coronary artery.

In this series 82 of the hearts were perfused from the right side and 68 from the left side of the heart; no difference was found in the results.

The disproportion between the sexes in the series reflects their respective admission-rates. Sex seemed to play no part in affecting results.

Normal Hearts

Table I shows that about 41% of these normal hearts had anastomoses classed as half or more, while 75% of the normal hearts in subjects older than 4 years had hearts so classified. The youngest individual showing substantial anastomosis was an infant aged 9 months (fig. 3). In all, 5 children under 5 years in this group showed anastomoses of grade half or more; this is an incidence of 11%.

Possibly the striking differences in the degrees of anastomoses present between those over and under the age of 4 years—75% with good anastomoses in the former group, compared with 11% in the latter—may be due to faults in technique in the work on tiny hearts. Until recently we have used narrow-bore soft-walled easily compressible cannulæ for children under 4 years; and these cannulæ may have exercised a poiseuille effect, as later work has shown a higher incidence of substantial anastomoses in tiny hearts where the narrow soft cannulæ have been changed to wide-bore steel cannulæ.

Table I includes certain hearts which were perfused into the left circumflex branch only or into the left descending branch only. This was done to investigate the possibility of anastomoses between major branches of the same coronary artery because, as with the technique of Schlesinger, our method of perfusing will not show anastomoses between branches of the same artery except by this special method. One striking result of this part-perfusion is shown in fig. 2; this heart was perfused via the left descending coronary branch only, the ligature round the cannula having been tied below the origin of the left circumflex branch. The resultant skiagram showed that the patient had substantial anastomoses both to the left circumflex branch on the same side and to the whole of the right side. This patient could well have maintained life on the supply to the left descending coronary branch alone.

Diseased Hearts

Of the 63 patients in this group 43 (69%) had chronic

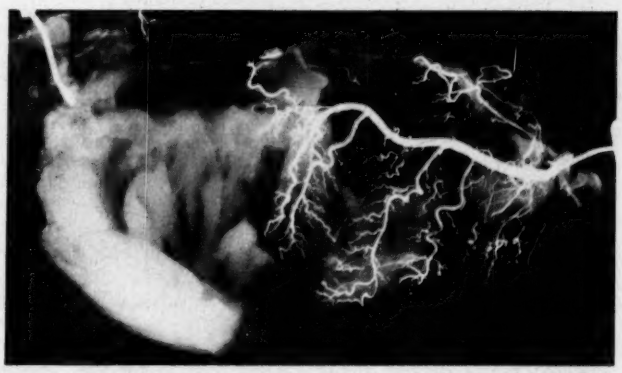


Fig. 4—Heart from patient with chronic ischæmic disease of heart but with no anastomosis.

ischæmic heart-disease. Of these 17 (40%) showed long-standing uncomplicated hypertrophy, almost always with ischæmic fibrosis of the myocardium; 11 (25%) showed hypertrophy and atherosclerosis of the coronary arteries as well, again almost always with ischæmic fibrosis of the myocardium; 9 (21%) showed severe atherosclerosis of the coronary arteries and/or the coronary ostia; and the remaining 6 (14%) showed severe chronic valvular disease. In the remaining 20 cases of this group of diseased hearts, the lesions mostly did not cause ischæmia of the myocardium; these lesions included pericardial effusion and enlarged or dilated hearts. Of the 63 patients with diseased hearts only 26% had anastomoses classified as half or over; in the subgroup of 43 patients with cardiac lesions associated with myocardial ischæmia only 23% had anastomoses of half or over. The findings are shown in table II.

Of the 43 patients found to have had chronic ischæmic heart-disease some had been in this hospital under our care one or more times before their last illness. Thus, one patient had been twice previously in hospital; the second time the diagnosis was myocardial infarction, which was confirmed at necropsy after the third admission. Although this patient was known to have had an ischæmic myocardial lesion of long standing, and there was gross calcification of the coronary arteries and the aortic cusps, the perfused heart showed only quarter-grade anastomosis. Another of the 43 had had two admissions to this hospital prior to death, on each occasion because of cardiac failure with cor pulmonale; but the skiagram showed nil anastomosis in the heart. Another patient who showed no anastomosis yet was known to have chronic ischæmic heart-disease had been in this hospital three times prior to death—on each occasion with cardiac failure due to aortic incompetence with gross myocardial hypertrophy.

Discussion

It is now believed that in the coronary circulation anastomoses follow the development of ischæmic myocardial disease, appearing where and when needed. But such anastomoses take some time to develop: Jones (1958) considers that a significant anastomotic flow will not develop in the heart in much under forty-eight hours, and Gregg (1950) claimed that full anastomoses may take one to three months to develop. Since myocardium deprived of its blood-supply is not likely to survive more than twenty minutes (Blumgart et al. 1940) it is not likely that such post-hoc anastomoses play any important part until some time after the onset of acute myocardial ischæmia of any significant degree.

In other ways also the present hypotheses appear inadequate. Gregg (1950), citing experiments on dogs, pointed out that there is "considerable natural variation in the ability of anastomotic circuits to develop . . . dogs which survive occlusion of a coronary artery without doubt represent a select group naturally endowed with a high resistance towards this type of procedure"; and he also stated that heredity is accepted by many workers as a significant ætiological factor in coronary heart-disease. Schlesinger (1940) also considered that the inherited patterns of coronary-artery distribution may be responsible for the familial and sex distribution of coronary heart-disease.

Our findings following perfusion of normal and of diseased hearts suggest a different explanation for the above facts. We have found anastomosis of significant degree—i.e., grade half or more—in the majority of normal hearts but only in one in about every four diseased hearts; fig 4 shows a heart with gross chronic myocardial ischæmia in which there is no anastomosis.

We therefore suggest that the majority of healthy people over the age of 4 years have a functionally important coronary anastomosis—i.e., our grade half or more. This finding is in keeping with the results of the small series reported by Prinzmetal et al. (1947); they perfused hearts from one ostium with glass beads of known diameter and found that anastomotic channels of arteriolar dimensions were present between the right and left coronary arteries in no less than 11 of 13 normal hearts perfused in this way. This naturally occurring anastomosis in normal hearts may possibly be an inherited characteristic, though not usually demonstrable until after infancy; this would explain the phenomenon of familial coronary heart-disease, such families presumably lacking an inherited anastomotic supply. In other words disease does not produce coronary anastomosis but appears despite, or because of lack of, a normal pre-existing anastomosis. This would also explain why some people are naturally endowed with a high resistance.

Summary

In an investigation into the blood-supply in normal and diseased hearts of 150 Bantu patients functionally significant anastomoses were found in 75% of normal hearts from patients over 4 years of age but in only 23% of hearts from patients with chronic ischæmic heart-disease.

Functionally significant anastomoses were found even in the hearts of some infants with no cardiac disorder.

The likeliest explanation is that a majority of healthy people have a functionally important inherited coronary anastomotic blood-supply; this inherited anastomosis probably protects some against ischæmic heart-disease and may modify ischæmic-heart disease in others.

For permission to publish this paper we thank Dr. J. Parker, Director of Hospital Services, Natal, and Dr. H. D. Tonking, Provincial Pathologist, Natal. We are indebted to Professor Fairbrother, of Natal University, for advice in matters physical and to Mr. M. H. Lello and Mr. S. Harvey for technical assistance.

REFERENCES

Blumgart, H. L., Schlesinger, M. J., Davis, D. (1940) *Amer. Heart J.* **19**, 1.
— — Zoll, P. M. (1941) *J. Amer. med. Ass.* **116**, 91.
Bourne, G. (1957) *Brit. med. J.* ii, 851.
Gregg, D. E. (1950) Coronary Circulation in Health and Disease. Philadelphia.
Gross, L. (1921) The Blood Supply to the Heart. London.
Jones, M. A. (1958) *Practitioner*, **180**, 159.
Laurie, W., Woods, J. D. (1958) *Lancet*, i, 231.
Mann, G. V. (1957) *Amer. J. Med.* **23**, 463.
Prinzmetal, M., Simkin, B., Bergman, R. C., Kruger, H. E. (1947) *Amer. Heart J.* **33**, 420.
Schlesinger, M. J. (1938) *ibid.* **15**, 528.
— (1940) *Arch. Path.* **30**, 403.

Addendum

This investigation still continues and the number of hearts perfused to date totals 350. Detailed analysis of the larger series is not yet complete, but preliminary surveys suggest that our views are supported by the later findings. In this later work complete anastomosis has been found in hearts from 3 newborn children under the age of 21 days. The youngest child to have coronary anastomosis of this grade was a premature Bantu baby 8 days old at death. Another child, aged 13 days, had complete anastomosis to the left circumflex and to the whole right side of the heart, shown by perfusion into the left descending coronary artery.

RENAL-VEIN CATHETERISATION AND VENOGRAPHY

A NEW TECHNIQUE

W. S. PEART
M.D. Lond., F.R.C.P.
PROFESSOR OF MEDICINE IN THE UNIVERSITY OF LONDON, AT ST. MARY'S HOSPITAL, W.2

DAVID SUTTON
M.D. Manc., M.R.C.P., F.F.R.
CONSULTANT RADIOLOGIST TO THE HOSPITAL

IN the course of studies on human renal function, it became necessary to collect renal venous samples from each kidney at close intervals of time. The usual technique for introducing a catheter into a renal vein has been to approach from above through an arm vein (Smith 1951, Actis-Dato and Angelino 1951, Dalla Palma and Servello 1956). To enter the right renal vein in this way is a straightforward procedure, since the vein comes off the inferior vena cava at a downward angle. Catheterisation of the left renal vein, however, is more difficult, because it comes off at right-angles to the inferior vena cava. Further, if admixture with blood from gonadal, suprarenal, or lumbar veins is to be avoided, the catheter must be advanced right up to the kidney, since these veins join the renal vein in its proximal half. We therefore devised a new technique whereby the bending of a catheter tip could be controlled during observation under the X-ray screen, and the renal veins were approached from below.

Method

The special catheter is simple to make, and consists of a modified American nylon catheter (no. 7, 8 or 9 are all suitable, no. 8 being the most generally useful). Fig. 1 shows the essential arrangement.

An ordinary cardiac catheter is cut down to 35 cm. long, with the usual syringe mounting at the end. A no. 5 nylon filament is threaded to an eyeless round-bodied needle and passed through the wall of the catheter 2·5 cm. from the tip, passing from inside to outside. A single knot cut short is sufficient to secure. Next, the needle is passed through the wall into the lumen again 3 cm. below, and the thread is brought out of the bottom end of the catheter. The needle is then passed back through the wall of the catheter from inside to outside, just above the syringe mounting. The end of the thread is looped and it will then be found that traction on it will bend the tip in the required direction.

Working the nylon thread in the holes will give the necessary sliding fit, so that the catheter can resume its natural shape when traction ceases. Care must be taken to have these holes through which the thread slides only a little larger than the thread in order to avoid leaks. These are usually very slight.

Technique

With local anæsthesia the saphenous vein is exposed below the saphenous ring; the catheter is introduced, and passed upwards. Under the X-ray screen the tip of the catheter is advanced to the level of the first lumbar vertebra and traction is applied on the thread so as to bend the tip and bring it up against the lateral wall of the inferior vena cava. When the catheter is pulled down gently, maintaining traction, the tip will usually spring into the

Fig. 1—Catheter with controlled tip. Traction on the nylon thread bends the tip of the catheter in the desired direction.

mouth of the renal vein. The thread is then released and the tip of the catheter can be advanced down the renal vein. On the right this will take it well out into the flank. On the left, the tip usually stops at the left vertebral margin. During all these procedures normal saline containing 1000 units of heparin per litre is dripped through the catheter. Blood can be drawn back rapidly, unless the tip is up against the vein wall, and in that case blood will flow if the catheter is gently withdrawn. The normal renal-vein blood can be recognised by its bright red colour, compared with that in the inferior vena cava. Incidentally, a hepatic vein can be entered readily, using the same procedure.

Renal Venography

For venography the patient is instructed and practised in the Valsalva manœuvre. He performs this immediately before the injection of 15 ml. of 70% 'Diaginol' or 70% 'Pyelosil'. The contrast medium is injected as rapidly as possible, the aim being to deliver the total dose within two seconds. A film is taken as the injection reaches its close. It is preferable to obtain several rapid

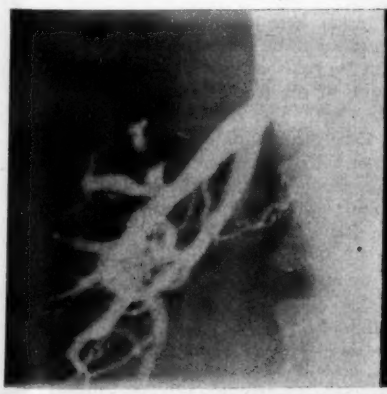


Fig. 2.

Fig. 3.

Figs. 2 and 3—Right renal venogram in two different cases showing small veins extending out into the kidney substance. Fig. 2 shows double renal veins.

Fig. 4.

Fig. 4—Left renal venogram showing catheter tip placed well along the lumen and beyond the termination of the gonadal and suprarenal veins.

serial films rather than a single film, but with the screening table used by us, this was rather difficult, and in practice the single film taken usually proved adequate for our purpose. The types of result obtained are illustrated in figs. 2–4.

Results

Bilateral renal vein catheterisation has been carried out successfully in 27 patients, with failure to enter one renal vein in 2, and failure to enter either renal vein in 1.

Discussion

Although placement of the catheter in the renal vein can be inferred by indirect observations, renal venography is the only means of getting absolute and accurate knowledge of the position of the catheter and of the drainage area from which the blood samples have been collected. Indirect evidence is provided by the fact that the renal veins are the only two veins which it is easy to enter below the level of the first lumbar vertebra and opposite the second lumbar vertebra using a no. 8 nylon catheter. Moreover, the characteristic direction of the vein may be appreciated by observing the lie of the catheter tip. Nevertheless our venographic studies have shown that a catheter tip which is thought to be in the renal vein may really be in a lumbar vein, or in a testicular vein (fig. 5). Thus venographic control appears desirable when renal-vein catheterisation is undertaken, particularly if there is the slightest doubt about the position of the catheter tip. Further, it is clear from our venographic studies that although renal-vein blood may form the main contribution to a blood sample on the left side this may also contain blood from systemic and suprarenal veins. Fig. 6 shows on the left side the frequent free connections between the lumbar and suprarenal veins, as well as with the gonadal vein. Our investigations have also shown that a catheter may enter one of the small tributary veins and that blood from only a small portion of the kidney may then be collected, as evidenced by the venogram (fig. 7). Thus the exact position and field of drainage from which a blood specimen is taken is accurately determined only by venography. On the left side it is clearly desirable to advance the catheter well along the renal vein to obtain a blood sample free from gonadal and suprarenal blood.

Fig. 5—The catheter tip lies in the mouth of a right sided vein passing vertically downwards and thought to be the right gonadal vein.

Fig. 6—Left renal venogram showing retrograde filling into the left suprarenal vein, left lumbar vein, and origin of the left gonadal vein.

Radiological visualisation of the renal veins has been coincidentally observed by Farinas (1947) during inferior-vena-cavography, and by Actis-Dato and Angelino (1951) who used small injections of contrast medium to show the exact position of the catheter tip in renal catheterisation from above. Renal venography by this route was studied in greater detail by Dalla Palma and Servello (1956). The latter authors have claimed that the procedure can be of use in the diagnosis of such renal lesions as renal tuberculosis and polycystic kidneys. They also included observations on the normal venography anatomy and on difficulties of interpretation during renal catheterisation and renal venography. It is doubtful, however, whether its use as a purely diagnostic method is justifiable in view of the simpler radiological techniques available.

Fig. 7—Right renal venogram. The tip of the catheter is too far distal and lies in a renal segmental vein.

The new technique here described enables arteriovenous extraction ratios to be performed on both kidneys for comparison; in the past both sides have not been very much used, because of the fear of admixture with non-renal blood on the left. The only complication in this series has been a local thrombophlebitis in the saphenous vein in one patient. With the new technique, bilateral renal-vein catheterisation has proved simpler and more consistently successful than with the previous technique of approach from above.

Summary

A new technique for bilateral renal-vein catheterisation, using a catheter with a controlled tip, is described.

Some results of renal venography are discussed.

REFERENCES

Actis-Dato, A., Angelino, P. F. (1951) *Cuore e Circolo*, **35**, 283 (cited by Dalla Palma and Servello).

Dalla Palma, L., Servello, M. (1956) *Pr. méd.* **7**, 150.

Farinas, P. L. (1947) *Amer. J. Roentengol.* **58**, 599.

Smith, H. W. (1951) The Kidney. New York.

REDUCTION OF SPUTUM VISCOSITY IN CHRONIC BRONCHITIS

WILLIAM ROBINSON
M.C., M.D. Leeds, M.R.C.P.
CONSULTANT CHEST PHYSICIAN

PAUL B. WOOLLEY
M.B. Manc., M.R.C.P.
ASSISTANT CHEST PHYSICIAN

R. E. C. ALTOUNYAN
A.F.C., B.A., M.B. Cantab.
OF BENGER LABORATORIES LIMITED

From the Thoracic Unit, Monsall Hospital, Manchester

THE three basic factors in the syndrome of chronic bronchitis are infection, bronchospasm, and abnormal sputum; and it is with the last of these that this paper is concerned. The mucosa of the bronchial tree is abnormal and the mucus-secreting glands, which are over-developed (Reid 1954), produce an abnormally viscid and tenacious mucus in excessive quantities. The stagnation of this mucus, which is a good medium for bacterial growth, leads to superadded infection and the production of mucopurulent or frankly purulent sputum.

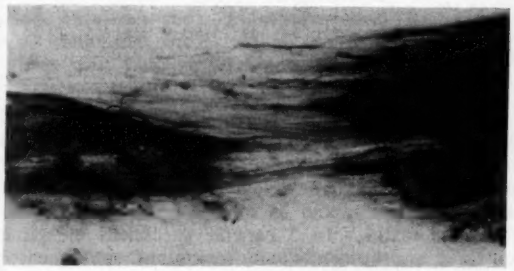


Fig. 1—Mucinous sputum showing hair-like fibrils of mucoprotein.

The viscosity of the mucoid sputum from the chronic bronchitic is proportional to its hydration and mucoprotein content. This material, suitably stained, can be seen to consist of long hair-like fibrils arranged in sheaves (fig. 1). In mucopurulent sputum the coarser desoxyribonucleprotein (D.N.P.) fibres are also present (fig. 2). In recent investigations efforts to reduce viscosity have devolved on the employment of detergent aerosols (e.g., 'Alevaire') or the aerosolisation of two enzymes—desoxyribonuclease (D.N.P.-ase) and trypsin.

In-vitro tests with these enzymes have shown that lysis of fibres, correlating with a reduction in viscosity, can be achieved with 0·05 mg. of enzyme per g. of sputum. In our initial experiments we came to the conclusion that there were several contraindications (discussed later) to aqueous aerosolisation—the main one being that we were unable to demonstrate any significant reduction in sputum viscosity. The administration of enzymes as a dry powder-smoke seemed to offer an alternative approach which was likely to be more practical and economical of enzyme. The size of the particles insufflated is important; for if they are too large they will not reach the peripheral bronchial tree, and undesirably large amounts of the powder may be deposited in the pharynx and trachea. The ideal particle size is around 3 μ. In our initial trials capsules were used containing D,N.P.-ase 5 mg. and chymotrypsin 5 mg., and the freeze-dried enzymes were passed through a 300-mesh sieve to obtain a fine powder. The particles varied considerably in size: the majority were found to be 1–10 μ in diameter; but the fewer 10–30 μ particles represented the largest proportion by weight. Chymotrypsin was used instead of trypsin as it proved to be less irritant. The 'Armour' penicillin insufflator was used, the powder being dispersed by compressing the bulb at the beginning of a deep inspiration. This method produced reasonable results with the more intelligent and cooperative patients who could inhale at the same time as the powder-smoke was produced by squeezing the bulb. But with most patients, owing to incoordination and wetting of the apparatus with saliva, this method was unsuitable. Accordingly, another apparatus was gradually evolved (fig. 3). By virtue of its design only inspiration through the apparatus forms the powder-smoke and manual coordination is not required. The average patient can empty a capsule with three to four deep breaths; dyspnœic patients can also operate the appliance satisfactorily, but require a few more breaths to empty a capsule.

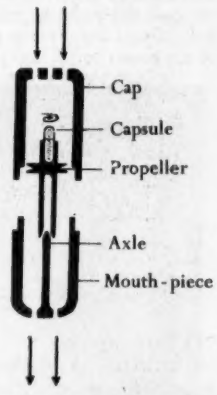


Fig. 3—Powder inhalation appliance.

By examining bronchoscopic aspirations and cough specimens for enzymatic activity on the fibrils in the bronchial secretion, we have confirmed that the powder gets well down the bronchial tree. Furthermore, in animal experiments using fluorescent-labelled chymotrypsin of similar powder characteristics, it was shown that particles reach the terminal bronchioles; but the concentration. or dose per unit area, deposited on the mucosa decreases towards the periphery. It must be remembered that the surface area of the bronchi increases after each subdivision so that increasingly large areas are available for powder deposition.

For trial purposes we decided to administer, by means of the appliance shown in fig. 3, a mixture of the two enzymes D.N.P.-ase and chymotrypsin, diluted with lactose and passed through a 300 mesh sieve. Owing to the wide range of particle size of this powder, its distribution was inevitably scattered over a large area.

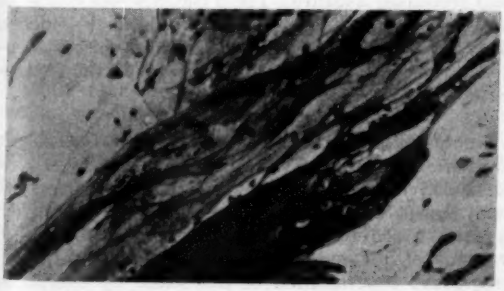


Fig. 2—Purulent sputum showing coarse fibrils of D.N.P.

Investigation

36 inpatients with chronic bronchitis were admitted to the trial; 15 were males and 21 females, and in each patient the bronchitis was of at least two years' duration. The only other pulmonary disease present was bronchiectasis in 12 of the

TABLE I—SPUTUM CHANGES OBSERVED IN TRIAL CASES

Viscosity (sputum pot)		Quantity		Nature	
Reduced	Unchanged	Increased	Unchanged	Unchanged	Blood-stained
31 (86%)	5 (14%)	14 (39%)	22 (61%)	34 (94%)	2 (6%)

patients. During the first three days after admission, each patient was put on physiotherapy and assessed clinically. The sputum was collected daily, measured, and examined for muco-protein and D.N.P. fibrils, colour, consistency, and relative viscosity. The relative viscosity gave an approximate guide to changes in viscosity during the period of investigation. 5 g. samples of sputum were collected at noon each day and stored at 4°C in 1 oz. McCartney bottles. For the determination, the bottles were arranged upright on a stand and then tilted simultaneously at various angles. By watching the fluid level and the rate of flow along the bottle it was possible to arrange the specimens in order of decreasing viscosity. Although this method was crude, results were reasonably consistent when care was taken to select specimens of sputum without saliva. For the next five days the enzymes were prescribed. One capsule was inhaled three times daily, each capsule containing 5 mg. of D.N.P.-ase and 5 mg. of chymotrypsin diluted with lactose.

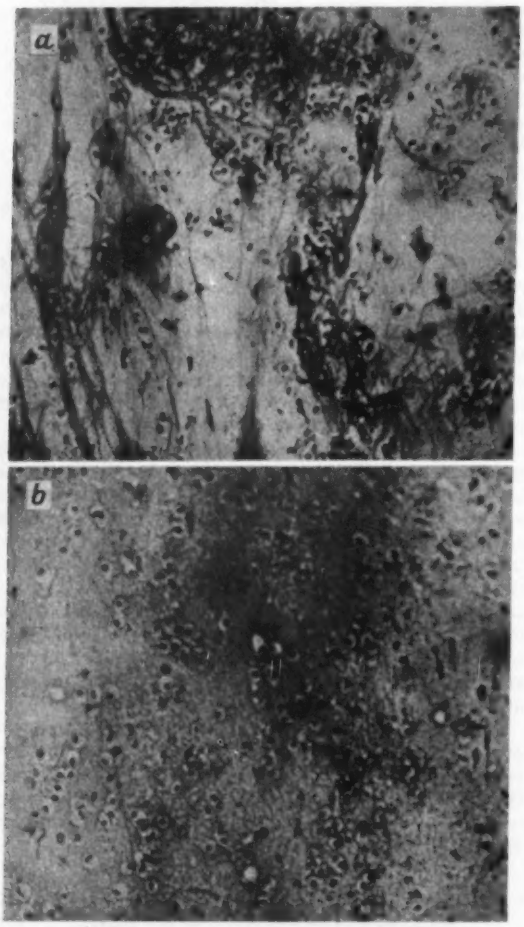


Fig. 4—Sputum (*a*) before and (*b*) 20 min. after inhalation of enzymes. In (*b*) there is complete lysis of fibrils; leucocytes remain. (Periodic-acid/Schiff, counterstained with 1% aqueous toluidine-blue.)

During and at the end of this period there was a further clinical assessment. The drugs were then suspended for three days and further specimens of sputum were examined. No other drugs were administered during the above period, but before the patient's discharge a course of antibiotics was given.

Results

Sputum Changes

The changes are summarised in table I. In 86% of the patients the sputum showed decreased viscosity, but in only 39% was there any increase in the amount expectorated. The fundamental character of the sputum was unchanged, except in 2 cases where it became blood-stained; this staining was not considered to be due to the enzymes.

Table II summarises the microscopical changes in the sputum—that is, the degree of lysis of the fibrils in treated

TABLE II—MICROSCOPIC EVIDENCE OF ENZYME ACTION

Source of sputum	No. of cases	Microscopic lysis of fibrils		
		Conspicuous effect	Doubtful result	No change
Sputum pot	36	24 (66%)	7 (19%)	5 (15%)
Cough specimen ..	22	22 (100%)	0	0
Bronchoscopic aspiration	3	3 (100%)	0	0

cases. It will be seen that in 66% there was a conspicuous effect. In 22 cases cough specimens of fresh sputum were produced twenty minutes after enzyme inhalation, preceded by gargling to wash any enzyme from the mouth and nasopharynx; and in each case conspicuous fibril lysis was found. In 3 patients specimens of sputum obtained by bronchoscopic aspiration, subsequent to enzyme inhalation, showed almost complete lysis. Fig. 4 shows complete lysis of both kinds of fibril in a cough specimen.

Clinical Assessment

Table III summarises the clinical changes in the 36 patients. In 67% there was subjective improvement, which in several was pronounced. Greater ease of expectoration was the most prominent change, and dyspnœa was decreased in most of the patients who improved. 44% had improved physical signs; in 56% the signs were more or less unchanged. The criteria adopted for changes in the physical signs were fairly rigid. In the group showing little change in the physical signs bronchospasm was a dominant factor. The 2 patients showing increased dyspnœa had increased bronchospasm, which was thought to have been brought about by the D.N.P.-ase fraction. This was confirmed some weeks later by spirometric tests before and after D.N.P.-ase inhalation, whereas similar tests with chymotrypsin were repeatedly negative. The 3 patients with hoarseness complained of this symptom only after they had been given a short period on double the dosage of the enzymes—it was not observed when patients were on the standard three capsules daily.

Discussion

Before these investigations were begun several pilot trials were carried out with aerolysing devices; but we concluded that administration of aqueous aerosol had many snags. It usually requires rather cumbersome apparatus which needs a good deal of attention. It is also wasteful of the substance atomised—firstly owing to progressive concentration of the solute by evaporation during the production of the aerosol, and, secondly,

TABLE III—SUMMARY OF CLINICAL RESULTS IN TRIAL CASES

Subjective impressions			Physical signs		Toxic effects		
Helpful	Unchanged	Worse	Improved	Unchanged	None	Hoarseness *	Increased dyspnœa
24 (67%)	10 (27%)	2 (6%)	16 (44%)	20 (56%)	31 (86%)	3 (8%)	2 (6%)

* These patients received double dosage.

owing to loss of activity of the enzyme solution, which has to be freshly prepared each time because activity drops off fairly rapidly. We have found surfactant detergent aerosols especially disappointing, probably because they have little effect on the fibrils. As Palmer (1957) says, they just hydrate viscid sputum. Various investigators (Salomon et al. 1954) claim considerable beneficial results from aerosol inhalations of D.N.P.-ase. Most recent published work, however, has been concerned with the action of trypsin on the mucoid fraction of the sputum (Limber et al. 1952, Unger and Unger 1953, Stevenson and Kinnier Wilson 1957). Although very encouraging results have been recorded, some workers (Farber et al. 1954) claim that the action of trypsin may be purely irritant, and patients have become wheezy after its administration (Forbes and Wise 1957). Chymotrypsin, on the other hand, although not quite so powerful a mucolytic, is far less irritant than either trypsin or acetylated trypsin; it therefore appears to have a higher therapeutic index. That its action is sufficiently powerful was proved by the microscopical changes in the sputum subsequent to its inhalation.

An advantage of the method of administration described here is that a combination of substances stable only in a dry form can be given simultaneously as a mixture; furthermore, the apparatus is compact and can be used conveniently by outpatients. As the purulent fraction of the sputum can usually be controlled satisfactorily by antibiotics—at least on inpatients—the D.N.P.-ase can be dispensed with and an antispasmodic substituted. In our investigation 67% of the patients experienced subjective improvement without the use of any antispasmodic. We believe that this figure could be improved considerably with effective antispasmodics which "potentiate" the action of the enzymes.

The toxic manifestations from these enzymes after a short period of treatment were not serious. 2 patients receiving double dosage experienced hoarseness, but this did not develop in any patient given clinically effective doses of 15 mg. of each enzyme daily. A more homogeneous powder with a particle size of approximately 3 μ would considerably reduce the concentration of powder deposited on the vocal cords.

The antigenicity of these two enzymes appears to differ. Whereas sensitivity to the D.N.P.-ase was observed in 2 cases, none of our patients have so far become sensitised to chymotrypsin. The possibility of sensitisation to chymotrypsin exists, but appears to be remote; 1 such case has been reported in a laboratory worker (Maclaren and Aladjem 1957). Several of our patients have inhaled chymotrypsin daily for six months without untoward incident, but the long-term effects of continuous therapy require further investigation.

Summary

36 inpatients with chronic bronchitis were treated by insufflation into the peripheral bronchial tree of powdered desoxyribonuclease and chymotrypsin.

The apparatus used for this insufflation is compact and convenient for use by outpatients.

Objective evidence of reduced sputum viscosity was obtained in nearly all cases during the period of treatment. 67% of the patients considered the treatment helpful.

Even better results are expected from a more homogeneous chymotrypsin powder with a particle size of about 3 μ, combined with a bronchodilator.

We should like to thank the staff of Benger Laboratories Ltd. for their cooperation, and the nursing staff of ward 17, Monsall Hospital, for their unstinted help with the patients.

REFERENCES

Armstrong, J. B., White, J. C. (1950) *Lancet*, ii, 739.
Farber, S. M., Gorman, R. D., Wood, D. A., Grimes, O. F., Pharr, S. L. (1954) *J. thorac. Surg.* **27**, 45.
Forbes, J., Wise, L. (1957) *Lancet*, ii, 767.
Habeeb, W., Reisser, H. G., Dick, F., Roettig, L. C. (1954) *Dis. Chest*, **26**, 408.
Limber, C. R., Reisser, H. G., Roettig, L. C., Curtis, G. M. (1952) *J. Amer. med. Ass.* **149**, 816.
Maclaren, W. R., Aladjem, F. (1957) *J. Allergy*, **28**, 89.
Palmer, K. N. V. (1957) *Lancet*, i, 611.
Reid, L. (1954) *ibid.* i, 275.
Salomon, A., Herchfus, J. A., Segal, M. S. (1954) *Ann. Allergy*, **12**, 71.
Stevenson, F. H., Kinnier Wilson, A. B. (1957) *Lancet*, ii, 820.
Unger, L., Unger, A. H. (1953) *J. Amer. med. Ass.* **151**, 707.

BRONCHODILATORS IN CHRONIC BRONCHITIS

WILLIAM ROBINSON
M.C., M.D. Leeds, M.R.C.P.
CONSULTANT CHEST PHYSICIAN

PAUL B. WOOLLEY
M.B. Manc., M.R.C.P.
ASSISTANT CHEST PHYSICIAN

R. E. C. ALTOUNYAN
A.F.C., B.A., M.B. Cantab.
OF BENGERS LABORATORIES LTD.

From the Thoracic Unit, Monsall Hospital, Manchester

IN a previous paper (Robinson et al. 1958) we described a method of reducing the viscosity of the sputum in chronic bronchitis by the inhalation of powdered enzymes from a specially designed inhaler. This method was found so convenient and effective that it was decided to extend its use to other drugs used in treating chronic bronchitis. Since bronchospasm is one of the most intractable features of this disease, the bronchodilator drugs appeared to be the obvious group to investigate.

An objective method was sought for measuring the degree of bronchospasm before and after treatment. Of the ventilatory function tests the forced expiratory volume at 1 sec. ($F.E.V._{1\cdot0}$) (Gandevia and Hughes-Jones 1957) was considered a fairly reliable index of the degree of "resistance" or spasm. The calculations were determined on a spirometer with a circumferential drum speed of 1 cm. per sec., and the average of six readings was ascertained on each occasion. After a few practice attempts the scatter of individual readings rarely exceeded $\pm 5\%$ of the average. We were particularly interested in this investigation to test the value of inhaled powdered isoprenaline and to discover whether its effect could be potentiated by the addition of some other drug.

Experimental Evidence

The minimum quantity of inhaled isoprenaline powder which can bring about maximal bronchodilatation was determined for powders of differing particle size produced by various procedures. Approximately 0·15 mg. of 1–5μ, or 0·3–0·5 mg. of a 1–10 μ, isoprenaline powder (passed through a 300 mesh sieve), diluted with lactose,

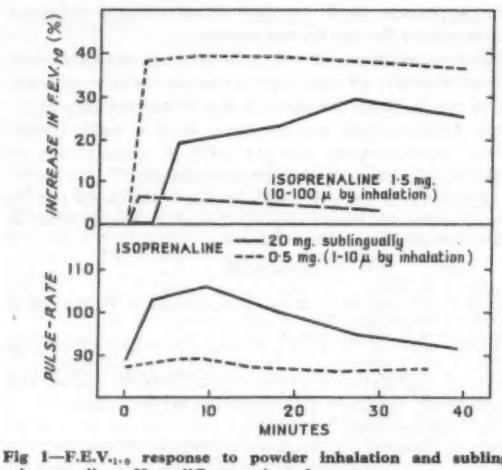

INCREASE IN F.E.V.1·0 (%)
ISOPRENALINE 1·5 mg. (10-100 μ by inhalation)
ISOPRENALINE — 20 mg. sublingually
--- 0·5 mg. (1-10 μ by inhalation)
PULSE-RATE
MINUTES

Fig 1—F.E.V.$_{1\cdot0}$ response to powder inhalation and sublingual isoprenaline. Note difference in pulse-rate.

produces a maximum effect in three minutes; a single inhalation from the appliance was sufficient to deliver the requisite dose, after which 70% of the maximal increase in F.E.V.$_{1\cdot0}$ occurred in twenty seconds. In contrast 1·5 mg. of a 10–100μ powder caused no significant change. This we interpreted as definite evidence that the smaller particles penetrate to the bronchioles and act locally, whereas the 10–100μ particles, by virtue of their size, cannot penetrate far enough to cause a direct local action.

20 mg. isoprenaline administered sublingually causes only a 60–70% maximal increase in F.E.V.$_{1\cdot0}$, which occurs twenty-five minutes later; there is a lag of five minutes before any effect is apparent. Fig. 1 shows a typical response following isoprenaline administration by the two routes to the same patient. The significant rise in pulse-rate with the sublingual route reflects the troublesome side-effects such as palpitation, dizziness, and tremor reported by many of our patients. There were no similar complaints after inhalation of isoprenaline powder in therapeutically effective dosage even from patients who were unable to tolerate the sublingual route.

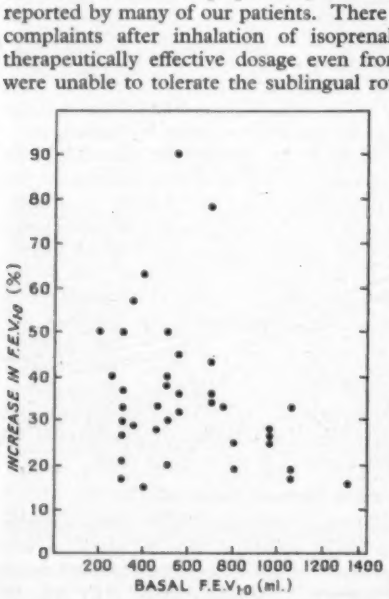


Fig. 2—Basal F.E.V.$_{1\cdot0}$ and percentage increase of F.E.V.$_{1\cdot0}$ to inhaled powdered isoprenaline in 30 patients.

30 male and 9 female patients were investigated, their average age being 45. They had all had a chronic productive cough—worse in winter—for two or more years, with dyspnœa on exertion and episodes of infected sputum. The results obtained in these patients after an optimal dose of isoprenaline powder (1–10μ) by inhalation are plotted in fig. 2. All patients showed a significant increase in their F.E.V.$_{1\cdot0}$. Nearly all reported almost immediate subjective relief with greater ease of expectoration. A significant increase in F.E.V.$_{1\cdot0}$ was maintained for one to three hours.

Protracted Isoprenaline Powder Inhalation Therapy

24 patients have been followed as outpatients for three to eight months at intervals of one to two weeks. Each day during the period of observation they inhaled, repeatedly, maximal bronchodilator doses of isoprenaline powder. Additional therapy (antibiotics, anti-histamines, prednisone) was also prescribed in some cases.

Particular attention was given to the possibility of tolerance to isoprenaline developing in these patients, who inhaled 4·5–15 mg. of isoprenaline daily for up to eight months. We confirmed the observations of Hume and Gandevia (1957) that the isoprenaline response is often related to the prevailing basal F.E.V.$_{1\cdot0}$. A change in the isoprenaline sensitivity of a patient can therefore be assessed only by comparing the responses obtained from the same basal F.E.V.$_{1\cdot0}$ values on every occasion. It is also important to ensure that no isoprenaline has been taken for at least four hours before a test, owing to the potentiation afforded by a previous dose administered within this period even when the basal readings are identical.

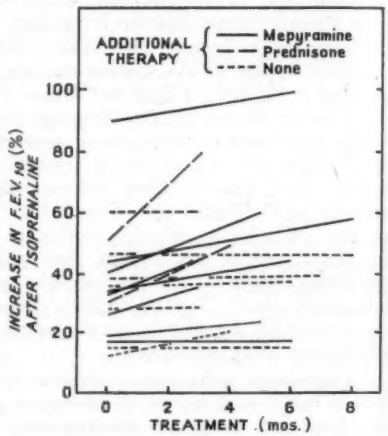


Fig. 3—Changes in F.E.V.$_{1\cdot0}$ response to isoprenaline during protracted therapy with isoprenaline powder inhalation alone, or combined with additional therapy. For each patient F.E.V.$_{1\cdot0}$ response was determined during identical basal F.E.V.$_{1\cdot0}$ conditions.

The percentage increase in F.E.V.$_{1\cdot0}$ after isoprenaline was assessed during the initial period of observation and on subsequent occasions at an interval of three to eight months when identical basal F.E.V.$_{1\cdot0}$ values prevailed. The results in 17 of the 24 patients under treatment are plotted in fig. 3. It was not possible to obtain this information on all patients, because some never reverted to their original basal F.E.V.$_{1\cdot0}$ values. It can be seen that 7 patients who received isoprenaline alone showed no significant variation in their isoprenaline response, whereas a 10% average increase occurred in 8 patients who had received continuous oral mepyramine therapy (300–600 mg. daily) in addition to isoprenaline. A 20% and 30% increase was observed in 2 patients who were on

TABLE I—RESPONSE IN THE F.E.V.$_{1\cdot0}$ TO PROLONGED ISOPRENALINE THERAPY

Additional treatment	No. of patients	Average increase in F.E.V.$_{1\cdot0}$ % response
None	7	1
Oral mepyramine	8	10
Prednisone	2	25

a short trial course of prednisone 10 mg. daily (table I). It must be concluded that there was no evidence of any reduction in the F.E.V.$_{1\cdot0}$ response developing in any of the patients who received isoprenaline therapy alone.

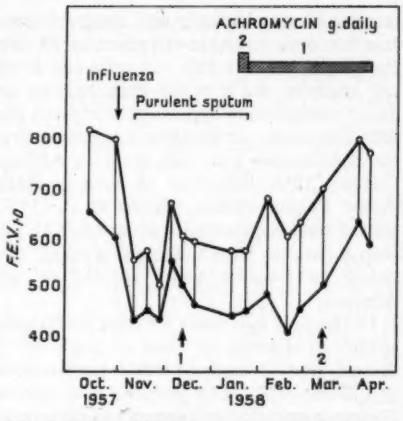


Fig. 4—Effect of infection and antibiotic therapy on typical bronchitic patient. Closed circle = basal F.E.V.$_{1\cdot0}$ value; open circle = F.E.V.$_{1\cdot0}$ after optimal dose of isoprenaline powder by inhalation.

The basal F.E.V.$_{1\cdot0}$ of many of these patients fluctuated considerably between July, 1957, and March, 1958, when they were under our observation. Fig. 4 shows the result of the influenza epidemic in a typical patient. After influenza he developed a mucopurulent sputum, his basal F.E.V.$_{1\cdot0}$ fell significantly, and there was a large reduction in his isoprenaline response. In these cases antibiotics can greatly improve this response, as is shown by this case. The sputum cleared five days after administration of antibiotics was started; when he was tested two weeks later his response to isoprenaline had apparently increased although his basal F.E.V.$_{1\cdot0}$ did not return to its normal value for a further two months. The isoprenaline response at arrow 1, when infection was present, can be fairly compared with the response obtained at arrow 2 when the infection had been controlled, as on both occasions the basal F.E.V.$_{1\cdot0}$ were identical. The isoprenaline response on the second occasion was considerably greater—presumably as a direct result of the reduction of œdema, vascular engorgement, and endobronchial secretions.

TABLE II—RESPONSE OF 19 PATIENTS TO MEPYRAMINE 25 MG. INTRAMUSCULARLY

Change in F.E.V.$_{1\cdot0}$	No. of patients
30% average increase	7 (37%)
10% " "	2 (10%)
No response	9 (47%)
Worse (bronchoconstriction)	1 (6%)

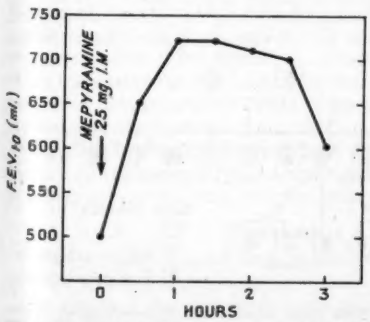


Fig. 5—Response in F.E.V.$_{1\cdot0}$ to intramuscular mepyramine.

Results of Mepyramine Therapy

The intrinsic bronchodilator action of parenteral mepyramine ('Anthisan') was first assessed in 19 patients after 25 mg. injected intramuscularly. Changes in F.E.V.$_{1\cdot0}$ were followed over several hours, and table II shows the results. 47% of the patients showed an increase in F.E.V.$_{1\cdot0}$, a clinically significant response being obtained in 37%. Fig. 5 shows the time course of events in one patient. This pattern has been confirmed repeatedly in other patients.

It is surprising that the period of bronchodilatation does not exceed three hours although the antihistaminic action of mepyramine lasts longer. This would appear to indicate that the bronchodilatation following mepyramine may not depend on its antihistaminic properties alone. It has already been shown in table I that patients given oral mepyramine continuously for over three months appear to have had some potentiation of their isoprenaline response although the average of 10% increase is not clinically very impressive. Fig. 6, however, demonstrates a dramatic change in one patient, aged 30, whose isoprenaline response and baseline improved repeatedly after oral and parenteral mepyramine.

In a further experiment the 24 patients in this series were each given oral mepyramine (300–600 mg. daily according to tolerance) for two to four weeks. Only 5 patients showed a significant improvement in their basal F.E.V.$_{1\cdot0}$, the increase averaging 170 ml. Nevertheless several other patients reported subjective benefit. 8 patients elected to continue with oral mepyramine, as they were convinced of the subjective benefit they obtained.

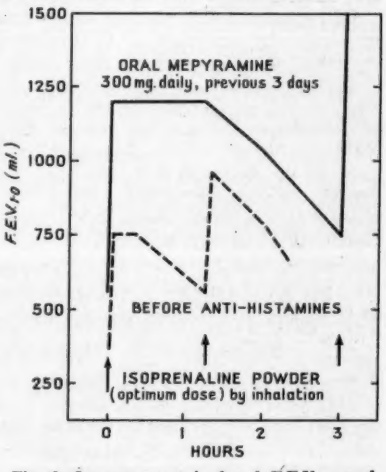


Fig. 6—Improvement in basal F.E.V.$_{1\cdot0}$ and isoprenaline response after oral mepyramine in one patient.

Discussion

Isoprenaline is a very useful drug in alleviating bronchospasm in the chronic bronchitic, and we are convinced that the best way of administering it is by powder inhalation. Provided that the powder particles are of suitable size —i.e., about 3μ—the response in the F.E.V.$_{1\cdot0}$ will be superior to that following a much larger dose given sublingually; moreover, unpleasant side-effects are not encountered. Brockbank and Pengelly (1958), in an investigation on asthmatic patients, obtained far better results by using inhaled powdered hydrocortisone than by using the same drug as an aerosol.

We believe that the anti-histamine mepyramine will "potentiate" the effect of isoprenaline in some bronchitic patients whose bronchospasm probably has an allergic basis. It is quite likely, however, that the degree of such "potentiation" will be much greater with the steroids and allied drugs. Kennedy and Thursby-Pelham (1956), in an investigation based on the expiratory flow-rate in asthmatic children, concluded that adrenaline plus oral cortisone gave far better objective results than adrenaline by itself; they thought that the action was probably "additive".

Bronchoconstriction requires energetic treatment in nearly all chronic bronchitic patients. It is convenient to regard the total bronchial obstruction in a given patient as the summation of two separate factors—an active component due to spasm of the bronchial muscles and a passive one due to engorgement, œdema, and endobronchial secretion. Temporary alleviation of the active element can be achieved efficiently and conveniently by isoprenaline inhalations. The treatment of the passive element is more complex, as there are probably many ætiological factors. Antibiotics, anti-histamines, enzymes, and steroids may all reduce the passive component under certain circumstances, thereby enhancing the action of isoprenaline. It is only by carefully assessing each chronic bronchitic that we can discover which combination of drugs is the most effective for him.

Summary

Practically all chronic bronchitics show an improvement in the forced expiratory volume after inhalation of powdered isoprenaline.

In 7 patients tested, protracted isoprenaline therapy brought about no reduction in the bronchodilator response to isoprenaline, determined by the forced expiratory volume at one second ($F.E.V._{1\cdot0}$).

Of 19 patients 47% showed an increase in $F.E.V._{1\cdot0}$ after intramuscular mepyramine. Oral mepyramine potentiates the isoprenaline response in some cases.

We should like to thank the staff of Benger Laboratories for their cooperation in this investigation, and the nursing staff of ward 17, Monsall Hospital, for their help with the patients.

REFERENCES

Brockbank, W., Pengelly, C. D. R. (1958) *Lancet*, i, 187.
Gandevia, B., Hughes-Jones, P. (1957) *Thorax*, **12**, 290.
Hume, K. M., Gandevia, B. (1957) *ibid.* p. 276.
Kennedy, M. C. S., Thursby-Pelham, D. C. (1956) *Brit. med. J.* i, 1511.
Robinson, W., Woolley, P. B., Altounyan, R. E. C. (1958) *Lancet*, ii, 819.

SICKLE-CELL ANÆMIA IN ADULTS AND ITS DIFFERENTIATION FROM SICKLE-CELL THALASSÆMIA

L. N. WENT
Ph.D. Utrecht
SENIOR LECTURER IN CHEMICAL PATHOLOGY

J. E. MACIVER
B.A., M.B. Cantab.
SENIOR LECTURER IN HÆMATOLOGY

DEPARTMENT OF PATHOLOGY,
UNIVERSITY COLLEGE OF THE WEST INDIES, JAMAICA

THERE is considerable uncertainty about the frequency of sickle-cell anæmia in adults. Neel (1951) stated that people with this disease have only a 20% chance of surviving to adult life. Vandepitte and Colaert (1955) and J. and C. Lambotte-Legrand (1955) regarded sickle-cell anæmia in adults in the Belgian Congo as very rare: they estimated the survival-rate at 1%. In Uganda Trowell et al. (1957) took a similar view, but Jacob (1957) put the survival-rate at 14%. Lehmann and Raper (1956) were inclined to doubt the existence of cases of homozygous sickle-cell anæmia in adults in Africa.

It is well known that sickle-cell anæmia and sickle-cell thalassæmia may present in very much the same way (Choremis and Zannos 1957), and they are often reported to be indistinguishable in the laboratory (MacIver et al. 1958).

All workers agree that only family studies can establish beyond doubt whether a case which resembles sickle-cell anæmia hæmatologically and electrophoretically is in fact true homozygous sickle-cell anæmia. Moreover, sickle-cell thalassæmia is as a rule clinically less severe than sickle-cell anæmia, and it is therefore easy to understand why many workers view reports of sickle-cell anæmia in adults with suspicion. In addition it is now well recognised that the thalassæmia gene can occur in Africans. Stijns and Charles (1956) described 35 cases of thalassæmia minor in the Belgian Congo, Norris et al. (1956) published a case of thalassæmia major in an adult Negro, and we have seen 4 patients with thalassæmia major (2 of whom were twins) in Jamaica and Trinidad in apparently pure Africans.

In the past two years we have investigated 114 cases of sickle-cell anæmia, 45 cases of sickle-cell hæmoglobin-C disease, and 11 cases of sickle-cell thalassæmia (MacIver and Went 1958). Our purpose is to present 49 cases of homozygous sickle-cell anæmia in persons aged 15 or over, and to compare them to cases of sickle-cell thalassæmia. This has enabled us clearly to differentiate between the two even without family studies. The methods used have already been described (Went and MacIver 1956).

Results

Of 114 cases of sickle-cell anæmia seen in the last two years 49 were 15 years of age or older. We have attempted to prove by family studies that they were truly homozygous.

We have been able so far to investigate 48 parents—including 10 parents of adult patients—out of a total of 212. (15 of our cases were members of 7 families.) Family studies are always difficult, and this is particularly so in the adult group where many of the parents are dead. In every case an S gene was demonstrated. In addition, 5 women with sickle-cell anæmia in our series had given birth to 12 living children. We were able to study 9 of these children, and again in every case we found the sickle-cell trait.

Fig. 1 shows the genealogical table of a large family in which 3 undoubted cases of homozygous sickle-cell anæmia in adults were found. Both parents, and all the surviving children of the propositus, have the sickle-cell trait. The blood-films of the parents give no indication of the simultaneous presence of a thalassæmia gene of poor penetrance, as has been described by Aksoy and Lehmann (1957); and in none of the remaining siblings did we find any evidence of thalassæmia. The 3 cases of sickle-cell anæmia in this family had typical hæmatological features—anæmia (Hb 8–9 g. per 100 ml.), reticulocytosis, and numerous fixed sickled cells in the stained blood-film.

We have previously described some of the cases of sickle-cell thalassæmia included in table I (MacIver et al. 1958, Went and MacIver 1958). We are now in a position to define clearly three groups in our series of 11 cases (table I).

Group 1.—In the Afro-Chinese group (cases 3, 7, and 11) the sickle-cell gene is contributed by the African mother and the thalassæmia gene by the Chinese father. (All 3 fathers

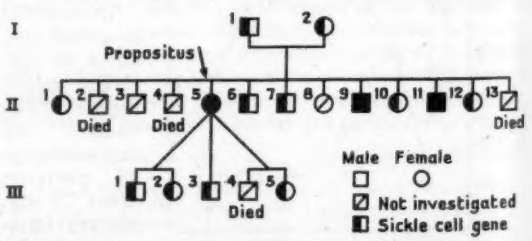


Fig. 1—Family tree with three adult cases of homozygous sickle-cell anæmia. I.2 also had six abortions. The children of II.5 are by three different fathers, who were not available for study.

TABLE I—MAIN LABORATORY FINDINGS ON PATIENTS WITH SICKLE-CELL THALASSÆMIA

No.	Age (years)	Sex	Hb (g. per 100 ml.)	Hb F (%)	Hb A (%)	Reticulocytes (%)	Film appearance				Electrophoretic pattern		Comments
							Fixed sickled cells	Target cells	Hypochromia	Basophil stippling	Father	Mother	
1	1½	M	9·1	12	Nil	6	Nil	+	+	Nil	A+S	S+F	Child of patient no. 10
2	3	F	..	..	20	..	Nil	++	++	Nil	..	..	..
3	4	F	8·4	6	Nil	19	Nil	++	++	+	A	A+S	Chinese father with thal. minor
4	9	F	10·9	6	22	..	Nil	+	+	Nil	A	..	..
5	12	M	11·8	1	27	..	..	..	..	..	..	A	Mother with thal. minor
6	15	M	10·2	25	Nil	4	Nil	+	+	Nil	A+S	A+F	Brother of patient no. 10
7	19	F	9·0	16	Nil	16	Nil	++	++	+	A	A+S	Chinese father with thal. minor
8	22	F	11·3	1½	25	3	Nil	+	+	Nil	A	A+S	..
9	23	F	6·9	6	15	..	Occasional	+	+	Nil	..	..	Died
10	26	F	12·6	27	Nil	5	Nil	Nil	Nil	Nil	A+S	A+F	Sister of patient no. 6, mother of patient no. 1, 5 children
11	28	F	10·6	9	Nil	25	Very few	++	++	+	..	A+S	Chinese father (dead). 1 child

were born in China.) There appears to be complete suppression of hæmoglobin A in the phenotype, and thus the electrophoretic pattern is indistinguishable from that seen in sickle-cell anæmia. The proportion of fœtal hæmoglobin was 6, 16, and 9% respectively. The appearances of a stained blood-film are striking, showing basophil stippling, target cells, and hypochromia (fig. 2). Fixed sickled cells are either very few or absent.

Group 2.—Cases in the Afro-Caucasian group (2, 4, 5, 8, and 9) were predominantly African with a varying amount of Caucasian admixture. 15–27% hæmoglobin A was found, and the levels of fœtal hæmoglobin were generally lower than in group 1. The blood-film (fig. 2) was much less abnormal, and basophil stippling was not seen.

Group 3.—In the African group (cases 1, 6, and 10) there was no evidence of Caucasian admixture. All 3 cases (in which there was no hæmoglobin A) belong to one family (Went and MacIver 1958). The propositus (case 10) has a hæmoglobin level of 12·6 g. per 100 ml. and a completely normal blood-film. The abnormal gene in this family is very unusual in that it also produces high levels (over 20%) of fœtal hæmoglobin in the heterozygous form. This is in contrast to the normal or very slightly elevated values usually found in thalassæmia minor. In addition, there are none of the usual hæmatological stigmata of thalassæmia minor. It is an open question whether the abnormal gene in this family is actually a thalassæmia gene.

Comparison of the blood-films from our cases of sickle-cell anæmia and sickle-cell thalassæmia reveals notable differences (fig. 2). Moderate to large numbers of fixed cells are the rule in sickle-cell anæmia, except under 5 years of age when they may be few or even absent.

This paucity of fixed sickled cells in younger patients has previously been noted by Trowell et al. (1957). With increasing age these fixed sickled cells become more and more obvious (MacIver and Went 1958). By contrast, we have never observed more than an occasional sickled cell in sickle-cell thalassæmia; and, in a typical case of sickle-cell thalassæmia, target cells and hypochromia are much more evident than in sickle-cell anæmia.

Discussion

In every case of sickle-case thalassæmia it was possible to make a tentative diagnosis in advance of family studies.

In group 1 the father in each family was Chinese, and the S gene has never been reported in the Chinese. In group 2 a varying amount of hæmoglobin A was found. In group 3 the condition caused neither symptoms nor hæmatological abnormalities in the propositus. The thalassæmia gene in combination with the S gene causes

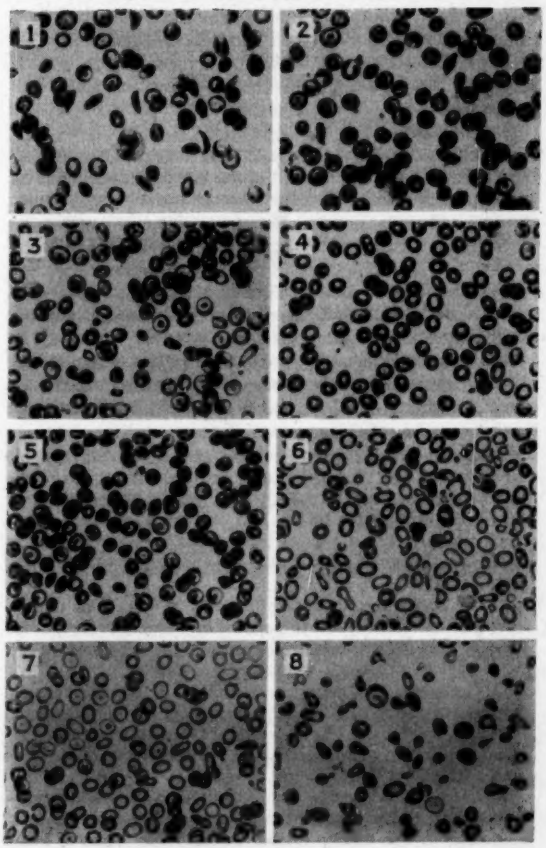


Fig. 2—Stained blood-films from representative patients with (1) sickle-cell anæmia; (2) sickle-cell hæmoglobin-C disease; (3) sickle-cell thalassæmia in Afro-Chinese; (4) sickle-cell thalassæmia in Afro-Caucasian; (5) homozygous hæmoglobin-C disease; (6) hæmoglobin-H thalassæmia; (7) thalassæmia minor; and (8) thalassæmia major.

TABLE II—MEAN HÆMOGLOBIN, RETICULOCYTE, AND FŒTAL HÆMOGLOBIN LEVELS ON OUR CASES OF SICKLE-CELL ANÆMIA, SICKLE-CELL THALASSÆMIA, AND SICKLE-CELL HÆMOGLOBIN-C DISEASE

—	—	Number of cases	Hb (g. per 100 ml.)	Hb (g. per 100 ml.)†	Hb F (%)	Reticulocytes* (%)
Sickle-cell anæmia	0–2	19	6·2	7·5	15·2	20½
	3–5	24	6·7	7·6	11·9	16½
Age-groups	6–15	27	7·1	7·6	7·4	18
	16–25	25	8·4	8·4	6·6	15½
	26 and over ..	19	7·0	7·0	8·0	9
	All ages	114	7·2	7·7	..	16½
	Range	..	1·6–10·3	5·2–10·3	2–30	0–35
Sickle-cell thalassæmia	Group 1	3	9·3	..	10	20
	Groups 2 and 3 ..	8	10·4	..	4 (*gr. 2*) 21 (*gr. 3*)	4½
Sickle-cell hæmoglobin-C disease	All ages	45	11·1	..	2·0	6
	Range	..	8·1–15·1	..	0·7–8	1–13

* Some very low reticulotyte-counts in young children were due to folic-acid deficiency.
† Omitting cases with values under 5 g. per 100 ml. (i.e., in obvious sickle-cell crisis).

a more severe hæmolytic process in the Afro-Chinese (group 1). This is evident from the lower hæmoglobin levels, the higher reticulocyte-counts, the complete suppression of hæmoglobin-A formation and the more abnormal blood-films (tables I and II, and fig. 2).

In all three groups the blood-films were quite different from those seen in sickle-cell anæmia. Moreover, in our cases of sickle-cell anæmia the mean hæmoglobin level is very much lower than in the 11 cases of sickle-cell thalassæmia.

If a fifth of our cases of sickle-cell anæmia were, in fact, examples of sickle-cell thalassæmia, then theoretically we would expect 5 of the 48 parents and 1 of the 9 children studied to be without an S gene. The fact that it was absent in none excludes, in our opinion, the possibility that sickle-cell thalassæmia accounted for a significant proportion of this series.

In the past two years we have seen only 3 deaths in patients with sickle-cell anæmia (1 child and 2 adults). This suggests that in Jamaica the survival-rate may be much higher than that reported from Africa. The results given in table II and the detailed hæmatological findings given elsewhere (MacIver and Went 1958) bring out some further features of this group of illnesses.

1. The mean hæmoglobin level in sickle-cell anæmia increases with age till adolescence, and decreases again in the oldest age-group (over 25 years). If, however, we leave out the cases with hæmoglobin of 5 g. per 100 ml. and lower—those which present with a typical sickle-cell crisis—then there is hardly any change in hæmoglobin level with age, except in the oldest age-group.

2. The mean fœtal hæmoglobin level in sickle-cell anæmia decreases significantly till the age of 6, whereafter it remains more or less constant but still very high compared to the mean level in sickle-cell hæmoglobin-C disease.

3. The average reticulocyte-count varies greatly in sickle-cell anæmia but seems to be significantly lower in the oldest age-group. This and the low hæmoglobin level in the same age-group suggest a diminished ability of the bone-marrow to compensate for the hæmolytic process.

4. Target cells are few in sickle-cell anæmia, although—in contrast to fixed sickled cells—they appear to be more numerous in this disease during the first four years of life.

5. In sickle-cell anæmia in the under-5 age-group, in which few sickled cells are found, the mean level of fœtal hæmoglobin is very high. This is evidence to support the argument that higher levels of fœtal hæmoglobin can exercise a protective effect against sickling.

We have already suggested (Went and MacIver 1958) the existence of a protective effect of high fœtal hæmoglobin levels in connection with case 10. The steady fall in fœtal hæmoglobin production with increasing age suggests the existence of a regulating mechanism. If this is so, and if high fœtal hæmoglobin levels do have a protective effect, then a means of stimulating the formation of this hæmoglobin might be of therapeutic value.

Summary

It is relatively easy in Jamaica to separate adult cases of sickle-cell anæmia from sickle-cell thalassæmia.

We present evidence to show that the great majority of our 49 adult cases of sickle-cell anæmia had the true genotype SS.

We have always been able to distinguish our cases of sickle-cell thalassæmia from those with sickle-cell anæmia before family studies. The blood morphology is appreciably different in the two diseases.

We were able to prove in one family that patients with sickle-cell anæmia can reach adult life and have children.

Our family studies in sickle-cell anæmia have also shown the presence of an S gene in all parents and in all children of SS homozygotes.

In the two years of our study we have seen only three deaths in our series of 114 cases of sickle-cell anæmia.

We think that in Jamaica the true natural history of the disease presents itself, whereas in Africa it may be obscured by parasitic and other tropical diseases. This will tend to eliminate early in life those whose resistance is weakened by severe anæmia.

In sickle-cell thalassæmia at least three groups of patients could be distinguished, depending on the race of the parent who had contributed the thalassæmia gene.

We are in receipt of a grant from the Colonial Office at the instance of the Colonial Medical Research Committee.

REFERENCES

Aksoy, M., Lehmann, H. (1957) *Brit. med. J.* i, 734.
Choremis, C., Zannos, L. (1957) *Blood*, **12**, 454.
Jacob, G. F. (1957) *Brit. med. J.* i, 738.
Lambotte-Legrand, J., Lambotte-Legrand, C. (1955) *Ann. Soc. belge Méd. trop.* **35**, 47, 53.
Lehmann, H., Raper, A. B. (1956) *Brit. med. J.* ii, 333.
MacIver, J. E., Went, L. N. (1958) *W. Ind. med. J.* **7**, 109.
— — Cruickshank, E. K. (1958) *Blood*, **13**, 359.
Neel, J. V. (1951) *Cold Spr. Harb. Symp. quant. Biol.* **15**, 141.
Norris, J. E., Hanson, H. H., Loeffler, R. K. (1956) *Arch. intern. Med.* **98**, 356.
Stijns, J., Charles, P. (1956) *Ann. Soc. belge Méd. trop.* **36**, 763.
Trowell, H. C., Raper, A. B., Welbourn, H. F. (1957) *Quart. J. Med.* **26**, 401.
Vandepitte, J. M., Colaert, J. (1955) *Ann. Soc. belge Méd. trop.* **35**, 457.
Went, L. N., MacIver, J. E. (1956) *W. Ind. med. J.* **5**, 247.
— — (1958) *Blood*, **13**, 559.

THE RELIEF OF PAIN IN SPASMODIC DYSMENORRHŒA BY BROMELAIN

CLIFFORD A. SIMMONS
M.A., B.M. Oxon., F.R.C.S., M.R.C.O.G.
CONSULTANT GYNÆCOLOGIST, MOUNT VERNON HOSPITAL AND THE RADIUM INSTITUTE; CHIEF ASSISTANT, CHELSEA HOSPITAL FOR WOMEN, AND QUEEN CHARLOTTE'S MATERNITY HOSPITAL, LONDON, W.6

PAPAIN and bromelain are proteolytic substances extracted from papaya fruit and the pineapple plant respectively, and since time immemorial, meat has been smeared with papaya to make it more tender (Hwang and Ivy 1951). In 1939 papain was first prepared as a crystalline extract by Balls and Lineweaver. In 1941 Balls, Thompson, and Kies extracted crystalline bromelain from pineapple fruit and in 1957 Hunter, Henry, and Heinicke described its preparation from pineapple stems.

Kurzrock (1948) investigated the mucolytic effect of papain on chronic cervicitis. Hunter, Henry and Civin (1957) used papain and bromelain in the diagnosis of the physiologically incompetent internal os using a technique described by Hunter and Henry (1955). Hunter and his colleagues investigated the action of these extracts on the human uterus. They reported that 40 patients with spasmodic dysmenorrhœa obtained immediate relief when treatment was given at the onset of the period, while in 24 women with secondary dysmenorrhœa the relief varied from poor to fair. They also demonstrated by hysterography that bromelain and papain relax the cervix. Their results were so striking that this trial was planned.

The bromelain obtained first was freeze-dried; later acetone-dried extracts were used. Both were in the form of a fine yellowish powder.

The samples were reputedly sterile but their plastic containers were not. Solutions were prepared in 50 ml. quantities in M/15 phosphate buffer at pH 5·5, each 50 ml. containing 0·075 g. bromelain. Cultures of the freshly buffered solutions grew both fungi and bacteria: they were therefore Seitz-filtered and then stored in 2 oz. sterile bottles.

Preliminary Investigation

Preliminary tests were made to confirm that bromelain was safe and to observe its effect on the cervix.

Proteolytic Activity

It seemed likely that the clinical effect of bromelain was related to its enzyme action. Various preparations were therefore tested for proteolytic activity as a guide to their total enzyme content.

Photographic plates were exposed for one hour at 37°C to digestion by standard drops of serial dilutions of the solutions. The plates were then washed and an estimate of the proteolytic activity was made from examination of the digested gelatin emulsion. It was found that proteolytic activity fell on storage of the solutions at either room temperature or 4°C, and that in both cases there was a 16-fold loss in a week and a 32-fold loss in a fortnight. There was little loss at −20°C for several weeks; but proteolytic activity was lost very rapidly on thawing at room temperature. Freeze-dried samples, on the other hand, retained their full activity on storage at room temperature; after reconstitution with water they lost their power only at the same rate as freshly prepared solutions.

The solutions stored at room temperature or at 4°C gradually developed a yellowish tint. The solutions stored at −20°C were colourless on thawing, but they rapidly became yellow at room temperature.

Toxicity Tests

Mice were injected intraperitoneally with Seitz-filtered 0·15% bromelain in phosphate buffer as made up for clinical use.

In the first batch of 12 mice, which received 0·5 ml. of the solution, 8 died within twenty-four hours, but 4 survived. Post-mortem examination showed gelatinous peritonitis and necrosis of the skin around the injection site. When the quantity injected was reduced to 0·1 ml. all the injected mice survived. 2 that were killed a week later showed no abnormality in the peritoneal cavity, but they had a small scar over the injection site. Thus it appeared that very large quantities given intraperitoneally produced severe peritonitis, but that slight contamination was not dangerous.

Method

In the first few cases solutions were used which had been stored in refrigerators; but their potency seemed to fall off as their proteolytic activity diminished. Freeze-dried preparations were therefore made: these only required the addition of water for immediate use. Tap-water was used in the treatment of dysmenorrhœa and sterile water in all the other cases. It was usually warmed, for temperatures up to 65°C are said to allow the enzymes to act with minimum loss of activity (Heinicke 1957).

The solution was poured into the vagina and allowed to bathe the cervix. This was exposed by a speculum for five to eight minutes. The vagina was then emptied, the cervix reinspected, and the speculum removed. In virgins it was sometimes difficult to introduce enough of the solution through a rubber catheter. A few patients treated themselves at home using a simple rubber bulb and a hollow glass tube.

Results

Table I shows the list of patients treated preoperatively in the course of the preliminary trial.

In all cases in which the cervix could be observed, it became softer and more vascular after treatment; it usually looked faintly blue like the cervix of early pregnancy. In most patients the external os became more patulous, and in 1 a cervical polyp that had been just visible before treatment was extruded. The softening of the cervix seemed to extend only as far as the internal os, which felt like hard rubber. In 2 cases where the uterus was evacuated at 7 and 9 weeks pregnancy the internal os was not easy to dilate. Another patient was 24 weeks pregnant when she was examined under anæsthesia during the application of the solution. The external os, which had not admitted a finger before treatment, then allowed one to be introduced, and the internal os, which was firm and tightly closed, could be palpated easily.

After treatment the vagina and cervix were found in all cases to be clear of discharge or mucus. Occasionally the cervix descended further down the vagina during treatment, as if the ligaments supporting the uterus had somewhat relaxed.

Hysterosalpingography

This investigation was carried out using 'Diodone' 30% or diodone with a dextran base.

After an initial film the cannula was removed and the bromelain applied. The cannula was then replaced, and more contrast medium was injected while a second film was exposed. There was usually some degree of dilatation of the cervical

TABLE I—PATIENTS IN THE PRELIMINARY TRIAL

Operation planned	Number treated
Dilatation and curettage	2
Total hysterectomy	1
Evacuation of the uterus for therapeutic abortion	2
Examination under anæsthesia at 24 weeks pregnancy	1
Hysterosalpingography	17
Total	23

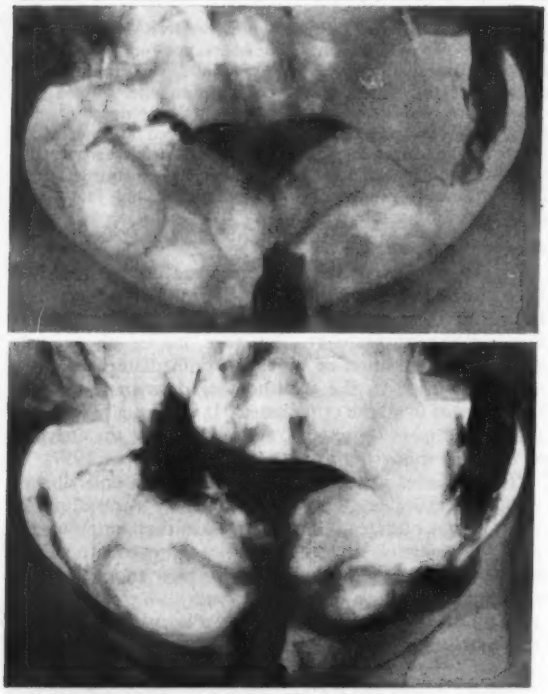


Fig. 1—Cervicohysterogram of a nulliparous patient: *above*, before treatment; *below*, eight minutes after bromelain was applied to the cervix. The cervix appears widely dilated as far as the internal os.

canal. Twice a screw-type cannula was used and left in situ, so that the bromelain could not penetrate into the canal. On both occasions the cervical canal appeared dilated after treatment.

1 patient had the cervicohysterogram repeated. The original film showed dilatation of the cervical canal under the influence of bromelain. The repeat film a week later showed the cervical canal almost back to its former dimensions.

Fig. 1 shows the diameters of the cervical canal in a nulliparous patient before and eight minutes after the application of bromelain.

The Treatment of Spasmodic Dysmenorrhœa

Table II shows the results of forty-eight treatments given to 30 patients with spasmodic dysmenorrhœa. All had complained of colicky pain reaching a climax with the onset of menstruation, and all but 4 vomited during menstruation: 16 actually fainted at that time. Only 2 were able to go out to work: the majority were compelled to stay away for one or two days. 6 had had previous treatment—including dilatation of the cervix and in some cases a curettage—with no permanent relief; œstrogens had been used in some cases with success.

TABLE II—THE RESULTS OF TREATMENT IN SPASMODIC DYSMENORRHŒA

Treatment	Number of patients	At work throughout period		Off work	
		Complete relief	Good relief	Slight relief	No relief
First	30	14	6	4	6
Second	12	7	2	3	–
Third	3	–	2	1	–
Fourth	2	–	2	–	–
Fifth	1	1	–	–	–
Total number of treatments	48	22	12	8	6

7 of the patients were married but nulliparous: 1, aged twenty-five, had had a baby without relief of her symptoms, which were later relieved by bromelain treatment. Table II shows that altogether thirty-four treatments were successful so that the patients could continue to work, although 12 of them had some discomfort. On eight occasions patients were unable to work for some time, but either the duration or the intensity of their pain was less, and there was none of the usual nausea, vomiting, or faintness. On six occasions patients obtained no relief whatever.

After a successful treatment, repeat treatment was not given until the patient had had a painful period. After the thirty-four successful treatments relief lasted for 4 cycles in three, 3 cycles in four, 2 cycles in nine, and 1 cycle in eighteen cases; but some patients have been treated too recently for the number of painless periods to be assessed.

The Optimum Time

The first 2 patients were treated within two hours of the onset of the period and they were relieved of all symptoms. It was then decided to treat patients at any convenient time but as near to the period as possible. Table III shows the day of the menstrual cycle on which treatments were given in relation to the results obtained.

The successful treatments with relief of all symptoms were given between the sixteenth day of the cycle and the onset of the period. All the successful treatments at the onset of the period were given within the first two hours,

TABLE III—THE TIME RELATIONSHIP BETWEEN TREATMENT AND THE MENSTRUAL CYCLE

Day of the menstrual cycle	M–1	M	5	10	16	17	18	19	20	21	22	24	25	26	27	28	29	Totals
Pain relieved* ..	4	12	–	–	1	1	–	1	2	4	1	3	1	–	1	–	1	32
Slight relief ..	–	2	–	1	–	–	1	–	–	–	1	1	2	–	–	–	–	8
No relief ..	3	–	1	–	–	–	–	–	–	–	–	–	–	1	–	1	–	6

M–1: Day before onset of period.
M: Day of onset of period.
* The day of onset was uncertain in 2 cases.

except one which was at the sixth hour. One treatment on the fifth day of the cycle gave no relief, and one treatment on the tenth day gave slight relief only; both patients had complete relief later when treatment was given just before the onset of the period. 1 patient was treated twelve and a half hours after the onset—too late to obtain relief. One cervicohysterogram taken a week after treatment with bromelain showed that the previously widely dilated canal had almost returned to its original diameters. It is probable therefore that the optimum time of treatment is just before the onset of the period, but that treatment may be effective in the latter part of the cycle, especially in patients who have relief for several cycles following one application.

The Effect of Age

Spasmodic dysmenorrhœa is alleged to be a self-limiting condition: it usually, but not always, ceases before the age of thirty. Most of the patients were under twenty-five: the 2 youngest were sixteen and the oldest forty-one. Their age seemed to have no influence on the results of treatment.

The Effect on the Period

There was no case of abnormal loss or flooding. Occasionally the period was altered in character, so that the loss was more equally distributed from day to day,

TABLE IV—PATIENTS WHO HAVE OBTAINED NO RELIEF FROM TREATMENT

No.	Timing of treatment	Possible reason for failure	Result of subsequent treatment
1	12½ hours after onset of period	Treatment given too late	Good
2	5½ hours after onset of period	Out-of-date solution used	Treatment not repeated
3	At onset of period	Virgo intacta	Complete relief
4	26th day of cycle	Virgo intacta	Treatment not repeated
5	5th day of cycle	Too early in cycle	Complete relief
6	27th day of cycle	?	Treatment not repeated

and sometimes the loss started without the patient being aware of it. In a few cases the onset was a few days early or late, but these variations seemed to be within normal limits.

Bromelain did not inhibit ovulation over several cycles: this was shown by the normal ovular pattern of the temperature charts of 3 patients.

Failures

Tables IV and V analyse the failures. Apart from obvious causes, some of the patients may have been suffering from undetected endometriosis, as in the series

TABLE V—TREATMENTS FOLLOWED BY SLIGHT RELIEF ONLY

Treatment	No.	Timing	Possible reason for failure	Result of subsequent treatment
First	7	At onset of period	?	Good relief
	8	25th day of cycle	?	Slight relief
	9	25th day of cycle	?	Slight relief
	10	24th day of cycle	?	Treatment not repeated
Second	8	23rd day of cycle	?	Treatment not repeated
	9	18th day of cycle	?	Not repeated
	11	10th day of cycle	Too early in cycle	Previous treatment later in the cycle had given good relief
Third	12	At onset of period	Solution used at home and spilled	Previous treatment had given good relief

reported by Ingersoll and Meigs (1948) and Te Linde (1953).

Other Types of Dysmenorrhœa

Eighteen treatments were given to 12 patients with secondary dysmenorrhœa.

In 10 patients with congestive dysmenorrhœa the pain or discomfort usually began a few days to two weeks before the period, and it was often associated with headaches. Colicky pain supervened sometimes with the onset of the loss. No pelvic abnormality could be detected in some, but others were under investigation for suspected tuberculosis or other disease. 2 patients had known endometriosis.

The results of treatment are shown in table VI. They suggest that bromelain can relieve some of the symptoms in secondary dysmenorrhœa if a spasmodic element is present.

Discussion

The Mode of Action of Bromelain

Bromelain stops the cramping pain of spasmodic dysmenorrhœa within a few minutes. Its mode of action is unknown, and it seems surprising that such a dilute solution, in contact with the vaginal mucosa and cervix for so short a time, could have such a rapid action. The active principle can be absorbed through the vagina and cervix, for it is effective if the cervical canal is blocked by the cannula used in hysterosalpingography. The occasional spill of the contrast medium after the bromelain has been applied suggests that it may also have some relaxant action on the fallopian tubes.

Bromelain appears to inhibit contraction of the smooth muscle of the cervix, and some of the therapeutic effects ascribed to its proteolytic activity may be due to this property. It is possible that other enzyme systems as described by Gortner et al. (1958) may be responsible for this action. If its action on the supporting ligaments of the uterus and on the fallopian tubes is confirmed, then it must be carried some distance from the point of application. In this series the cervix relaxed only as far as the internal os, which—with 2 exceptions—remained firm or

TABLE VI—RESULTS OF TREATMENT IN SECONDARY DYSMENORRHŒA

Type	Number of patients	Able to work throughout period		Off work	
		Complete relief	Good relief	Slight relief	No relief
Congestive ..	10	–	2	3	5
Endometriosis ..	2	–	1	–	1

was not more than slightly dilated. The 2 exceptions were patients who gave a history of repeated miscarriages and in whom a physiologically incompetent internal os had been diagnosed (fig. 2). Whether this relaxant action in these cases is specific remains to be determined.

It is difficult to see how bromelain can give relief from spasmodic dysmenorrhœa through several cycles if it acts only by inhibiting contraction of the smooth muscle of the cervix and by allowing easy passage to the menstrual flow. Perhaps it affects connective tissue as well as

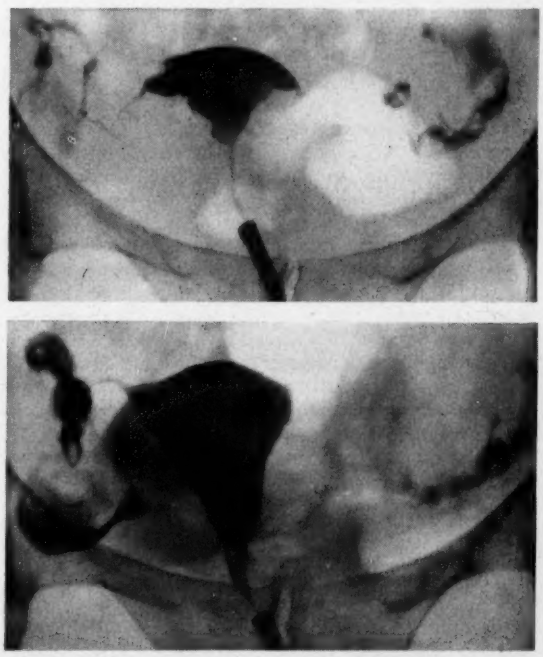


Fig. 2—Cervicohysterogram of a patient who suffered from repeated miscarriages possibly due to an incompetent internal os; *above*, before bromelain was applied; *below*, after treatment. Although the uterus is more erect after treatment, the dilatation of the cervical canal, with no indentation in the region of the internal os, is clearly seen.

muscle or possibly the nerves may be affected and may take time to recover.

Toxic Effects and Complications

Crude bromelain extracts can attack living tissues, but Hunter (1957) found that the reprecipitated fraction caused no complications. In this series treatment covered a period of ten months but the long-term effects of these enzymes on the cervix are not yet known and they therefore must be used with caution. Accidental contamination of the peritoneal cavity is unlikely to be harmful: indeed, papain solutions have been used to prevent the formation of peritoneal adhesions (Ochsner and Storck 1936, Elliott and Meleney 1937). Hwang and Ivy (1951) have reported allergic reactions after repeated exposures to papain, but up to five treatments have been given to individual patients with no ill effects.

Initial flooding after treatment as was described by Hunter, Henry, and Heinicke (1957) was not encountered.

Other Possible Uses

Bromelain and papain have been of value in cleansing the vagina and cervix of debris and mucus, and they might be useful in clearing the cervix of " hostile " mucus before artificial insemination. However, when bromelain solution was gently mixed with cervical mucus containing actively motile spermatozoa these soon became inactive.

There is no evidence that bromelain acts as an abortifacient: its application did not make dilatation of the internal os easier.

Summary

Bromelain, an extract of pineapple stem, has been used over a period of ten months on 65 patients. It has been used on eighty-nine occasions without complications.

23 patients received treatment before operation or before cervicohysterography. The clinical effects, within a few minutes of application, were softening of the cervix with increased vascularity. The cervical canal, as observed by radiography and confirmed by palpation, dilated as far as the internal os. This remained firm except in 2 patients in whom it was physiologically incompetent. Relaxation of the uterine supports may account for the descent of the cervix in some cases. The vagina and cervix were cleared of mucus or discharge by the treatment.

30 patients with spasmodic dysmenorrhœa received forty-eight treatments. The results were good on forty-two occasions. There was no relief on six occasions, but probable reasons could be suggested for five of these failures.

10 patients with congestive dysmenorrhœa and 2 patients with endometriosis received eighteen treatments. They obtained some relief if a spasmodic element had been present.

The optimum time of application was just at the onset of, or shortly before, the period.

In some cases relief persisted for as many as four cycles after treatment.

Ovulation was not inhibited by treatment. There was no evidence that bromelain would be of use as an abortifacient: evacuation of the uterus was not made easier by its application.

The dramatic effect of bromelain on the colicky pain at the onset of the period is due, at least in part, to relaxation of the smooth muscle of the cervix. Possible modes of action are discussed.

My thanks are due to Dr. A. C. Hunter; to Dr. R. M. Heinicke, and Dr. G. Felton of the Hawaiian Pineapple Company for their encouragement and for a supply of acetone-dried bromelain, and to Dr. R. A. Miley of British Schering Company for a supply of the original freeze-dried bromelain used by Dr. Hunter and his colleagues. The solutions were prepared and the animal experiments carried out at the Bernhard Baron Memorial Research Laboratories, Queen Charlotte's Maternity Hospital. I am very grateful to Dr. J. Murray who performed the animal experiments and who assisted me with the paper, and to Mr. E. C. Clark for preparing the bromelain and making the assays. My thanks are also due to the staffs of Chelsea Hospital for Women, Queen Charlotte's, and Mount Vernon Hospitals for allowing me to treat their patients, and to Dr. J. H. Smitham for the salpingograms taken at Chelsea.

REFERENCES

Balls, A. K., Lineweaver, H. (1939) *J. biol. Chem.* **130**, 669.
— Thompson, R. R., Kies, M. W. (1941) *Industr. Engng Chem.* **33**, 950.
Elliott, R. H. E., Meleney, F. L. (1937) *Surgery*, **1**, 785.
Gortner, W. A., Kent, M. J., Sutherland, C. K. (1958) *Nature, Lond.* **181**, 630.
Heinicke, R. M. (1957) Personal communication.
Hunter, R. W. (1957) Personal communication.
— Henry, G. W. (1955) *Fertil. Steril.* **6**, 68.
— — Civin, W. H. (1957) *Amer. J. Obstet. Gynec.* **73**, 875.
— — Heinicke, R. M. (1957) *ibid.* p. 867.
Hwang, K., Ivy, A. C. (1951) *Ann. N.Y. Acad. Sci.* **54**, 161.
Ingersoll, F., Meigs, J. V. (1948) *New Engl. J. Med.* **238**, 357.
Kurzrock, R. (1948) *Amer. J. clin. Path.* **18**, 491.
Ochsner, A., Storck, A. (1936) *Ann. Surg.* **104**, 736.
Te Linde, R. W. (1953) Operative Gynæcology; p. 507. Philadelphia.

FATAL PULMONARY CHANGES DURING THE MEDICAL TREATMENT OF MALIGNANT HYPERTENSION

T. HILDEEN
M.D. Copenhagen.

A. R. KROGSGAARD
M.D. Copenhagen.

BJ. VIMTRUP
M.D. Copenhagen

From Medical Department C and Institute of Pathology, Bispebjerg Hospital, Copenhagen, Denmark

IN 1953 Morrison reported that 3 patients with malignant hypertension developed severe dyspnœa, due to pulmonary infiltration, while under treatment with parenteral hexamethonium. A more detailed account of these cases was given by Doniach et al. (1954); and others were described by Corcoran et al. (1954), Goldsmith et al. (1955), Hood et al. (1954), and Robillard et al. (1955). More recently Perry et al. (1957) reported 8 cases and thoroughly investigated this condition. We present here a similar case.

Case-report

Clinical History

In 1948 a 28-year-old woman developed hypertension. By September, 1955, her blood-pressure was 210/130 mm. Hg; she had grade-III changes in her fundi (Keith and Wagener's classification); and her blood-urea was 42 mg. per 100 ml. The electrocardiogram showed left axis-deviation and inverted T-waves in all standard leads. The heart was slightly enlarged. Treatment with pentolinium and hydrallazine had to be abandoned because of untoward side-effects.

She was first admitted to hospital in April, 1956, when her main complaint was severe morning headaches. Her blood-pressure was 260/160 mm. Hg; ophthalmoscopy showed papilloedema, recent and old hæmorrhages, and " cotton-wool " exudates; and she had albuminuria. Her hæmoglobin was 90%, the serum-creatinine 1·7 mg. per 100 ml., and the 24-hour endogenous creatinine-clearance 36–37 and 34 ml. per min. The chest X-ray showed cardiac enlargement but no pulmonary congestion, and the intravenous pyelogram was normal.

She was put on reserpine, pentolinium, and hydrallazine by mouth and treated as an outpatient; but her blood-pressure continued to fluctuate. In March, 1957, the reserpine had to be discontinued because it was apt to make her weep. The dose of hydrallazine was slowly increased to 100 mg. four times daily, but the dose of pentolinium could only be raised to 80 mg. four times daily because of its unpleasant side-effects—

Fig. 1—Anteroposterior and left lateral chest X-ray taken on Aug. 13, 1957: " cotton-wool " densities in both lungs and cavitation suspected in the left lung.

constipation, shivering, and œdema. Mecamylamine ('Mevasin') was tried but it caused retention of urine : and chlorisobdamine (' Ecolid ') produced abdominal pain. Nevertheless, her papillœdema resolved and her renal function was maintained.

On readmission, on July 30, 1957, she had severe dyspnœa, orthopnœa, and œdema of the ankles. Her blood-pressure was 220/140 mm. Hg. Chest X-ray showed severe pulmonary congestion, mainly in the hilar regions. She was treated with mercaptomerine without effect; and, on the assumption that the lung changes were an allergic response to the hypotensive drugs, prednisone was tried. Repeat radiograms, however, showed more cotton-wool shadows (fig. 1) and an area in the left lung suggestive of cavitation. As pulmonary tuberculosis

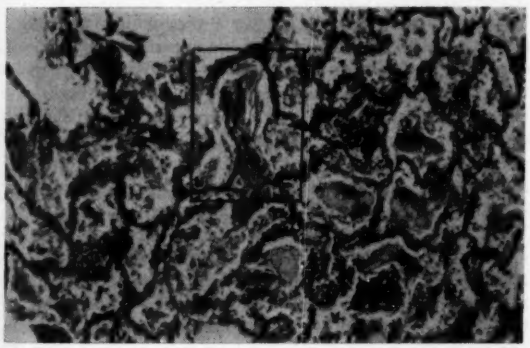


Fig. 2—Photomicrograph showing thickened interalveolar septa. (×80.)

could not be excluded, streptomycin, *p*-aminosalicylic acid, and isoniazid were also given, but without improvement. The patient died on Aug. 20, 1957.

Postmortem Findings

The *heart* weighed 480 g. and showed left ventricular hypertrophy.

The *kidneys* had a local hæmorrhagic surface and the cortices were narrowed. Microscopically there was advanced arteriolar sclerosis but no arteriolar necrosis.

The *lungs* were of normal size, and their surfaces were smooth. Only the peripheral zones contained air, the rest was firm. The smaller bronchi contained a little frothy, serous fluid; but there was no massive pulmonary œdema. No cavity and no evidence of tuberculosis was found. Microscopically all parts, except the periphery, showed gross increase in interstitial tissue (figs. 2–4). The alveolar septa were thickened: they contained tortuous dilated capillaries, proliferating fibroblastic tissue, and scattered masses of fibrinoid substance. Only few of the alveoli were obliterated, but many were reduced to mere slits by dome-shaped excrescences of fibroblastic tissue (fig. 3). The alveolar epithelium was swollen and partly covered with fibrin deposits. White blood-cells were not conspicuous and there were no iron-containing " heart-failure " cells. The blood-vessels were normal.

Discussion

Only 22 cases of pneumonitis complicating the medical treatment of hypertension have been reported. All but one of the patients had had malignant hypertension, and in all but the present case hexamethonium had been used. We gave pentolinium. Hydrallazine (' Apresoline ') had been given, besides ganglion-blocking agents, in about half the previously reported cases; and some had had pentolinium as well as hexamethonium. In none of them had the hypertension been well controlled.

Fig. 3—Section of area shown in fig. 2: alveolus almost filled with dome-shaped mass of fibroblastic and collagen tissue. (×280.)

The lung complication develops suddenly or gradually over a few weeks and shows itself by increasing dyspnœa. The prognosis is bad: all patients, except one of Morrison's, died within a few weeks.

The X-rays show diffuse or nodular infiltration of both lungs, starting from the hilar regions. At necropsy the naked-eye appearance of the lungs may suggest simple congestion, but microscopical examination reveals the characteristic changes which involve the interalveolar septa. It is probable that the earliest change is infiltration by lymphocytes and plasma-cells and that these cells are later replaced by proliferating fibroblastic tissue (Morrison 1953). A hyaline membrane may develop along the alveolar walls; and, if there is much exudation, the microscopical picture may suggest uræmia.

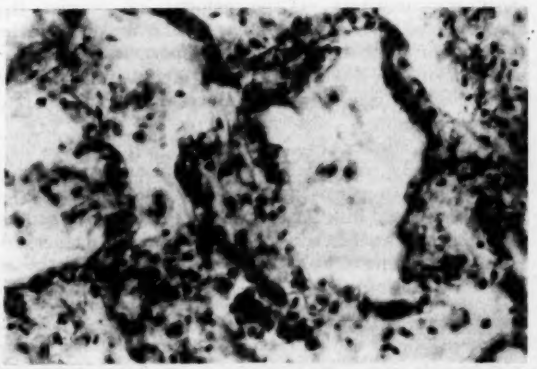


Fig. 4—Photomicrograph of fibroblastic proliferation and leucocytic and lymphocytic infiltration of the interalveolar septa. (×280.)

Opinions differ about the ætiology. Doniach et al. (1954) believed that repeated attacks of left-sided heart-failure, with partial recovery under hexamethonium therapy, were responsible: the fluctuating blood-pressure would thus be an important aggravating factor. Perry et al. (1957), on the other hand, blamed hexamethonium itself. They described postmortem findings in three groups of cases—those who died from malignant hypertension without treatment with hexamethonium, those who had had hexamethonium therapy, and those who had mitral stenosis. The lung changes, which they called " fibrinous pneumonitis ", were commonest in the second group; and they had developed at much lower blood-urea levels than in the first group. In the mitral-stenosis group there were very few cases of pneumonitis. Since our patient did not have hexamethonium, the pulmonary changes cannot be regarded as a specific complication of the former drug.

Summary

A woman of 36 developed dyspnœa while under medical treatment for malignant hypertension. She died three weeks later. Satisfactory control of her blood-pressure had never been achieved. She had received reserpine, hydrallazine, and pentolinium, but no hexamethonium. For brief periods she had also had mecamylamine and chlorisondamine.

The radiological and postmortem features of the fatal lung complication are described: they were similar to the fibrinous pneumonitis reported by others as a rare complication of hexamethonium therapy.

REFERENCES

Corcoran, A. C., Dustan, H. P., Taylor, R. D., Page, I. H. (1954) *Amer. J. Med.* **17**, 383.
Doniach, I., Morrison, B., Steiner, R. E. (1954) *Brit. Heart J.* **16**, 101.
Goldsmith, H. J., Beaver, D. W., Lambert, H. P. (1955) *Lancet*, i, 371.
Hood, B., Björk, S., Falkheden, T. (1954) *Svenska Läkartidn.* **51**, 1169.
Morrison, B. (1953) *Brit. med. J.* i, 1291.
Perry, H. M., O'Neal, R. M., Thomas, W. A. (1957) *Amer. J. Med.* **22**, 37.
Robillard, R., Riopelle, J. L., Adamkiewicz, L., Tremblay, G., Genest, J. (1955) *Canad. med. Ass. J.* **72**, 448.

Preliminary Communication

INTESTINAL ABSORPTION OF RADIOVITAMIN B_{12} BOUND IN PIG LIVER

Heathcote and Mooney [1] have described a peptide which they claim facilitates the absorption of vitamin B_{12} from the intestine. Their results were discussed by Latner,[2] and further experiments with this substance, including exact measurements of the amount of vitamin B_{12} absorbed, will be of great interest. To understand the function of intrinsic factor it is important to find out whether vitamin B_{12}-binders exist which do not originate from gastric juice or gastric mucosa, but are able to enhance vitamin B_{12}-absorption.

Previous studies by our group [3 4] indicated that, physiologically, vitamin B_{12} in man is excreted mainly in the bile. In normal subjects, however, some of the vitamin excreted into the bile seems to be reabsorbed by the intestine, and recently [5] it was found that such re-absorption seems to take place also in some patients with megaloblastic anæmia and disturbed absorption of exogenous vitamin B_{12}. This could be due to the effect of a vitamin B_{12}-binding substance present in bile, which might promote absorption of the vitamin.

1. Heathcote, I. G., Mooney, F. S. *Lancet*, 1958, i, 982.
2. Latner, A. L. *ibid.* p. 1077.
3. Gräsbeck, R., Nyberg, W., Perman, G., Reizenstein, P. *Acta phys. scand.* 1957, **42**; suppl. 145.
4. Gräsbeck, R., Nyberg, W., Reizenstein, P. *Proc. Soc. exp. Biol. N.Y.* 1958, **97**, 780.
5. Reizenstein, P. Swedish Medical Society; December, 1957. (*Nord. Med.*: in the press.)

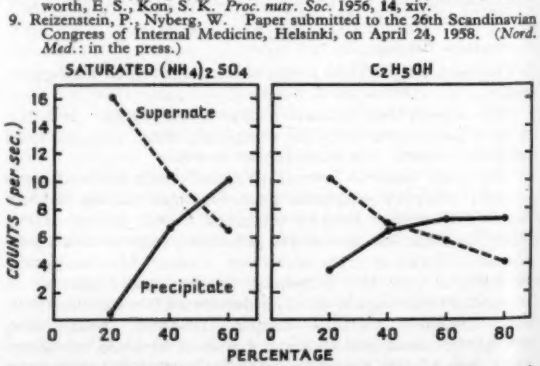
INTESTINAL ABSORPTION OF CRYSTALLINE AND LIVER-BOUND B_{12}

Case	Normal controls: B_{12}-^{60}Co in liver		Normal controls: Crystalline B_{12}-^{60}Co		Case	Pernicious anæmia: B_{12}-^{60}Co in liver		Pernicious anæmia: Crystalline B_{12}-^{60}Co	
	B_{12} given (μg)	% absorbed	B_{12} given (μg)	% absorbed		B_{12} given (μg)	% absorbed	B_{12} given (μg)	% absorbed
1	28	48	40	18·0	3	33	69	..	..
2	28	54	40	1·0	7	14	40	20	(21*)
4	29	15	50	1·3	8	35	45	50	4·0
5	27	25	50	0·9	9	35	91	40	8·5
6	29	21	50	0·6					
Mean absorption		32·6		4·4			61·2		6·2
S.E. of mean		7·58		1·28			11·75		..

* Some 24-hour fæces samples lost.

In one recent experiment [9] pig liver containing native radiovitamin B_{12} was obtained by daily parenteral administration of radiovitamin B_{12} to a pig, which was killed after a month. The liver contained approximately 6 mμg. vitamin B_{12}-^{60}Co and approximately 560 mμg. non-labelled B_{12} per g. of wet tissue. Of the vitamin in the liver approximately 88 ± 3% was non-dialysable. Samples of this liver were fed to five healthy volunteers and to four patients with untreated pernicious anæmia (i.e., megaloblastic anæmia, pathological vitamin-B_{12} absorption test [Schilling], no clinical signs of sprue or tapeworm). Fæces were collected for 7 days and the excreted radioactivity was measured. Eight of the patients then received comparable though somewhat larger amounts of crystalline radiovitamin as a control test. Absorption of liver B_{12} was not significantly higher in the controls than in the cases of pernicious anæmia, and more of the bound B_{12} than of the crystalline vitamin (see table) seemed to be

6. Report of National Institute for Research in Dairying (Reading) for 1953; p. 93.
7. Chow B. F., Davis, R. L. *Nutrition. Symp. Series*, 1952, **5**, 17.
8. Coates, M. E., Gregory, M. E., Harrison, G. F., Henry, K. M., Holdsworth, E. S., Kon, S. K. *Proc. nutr. Soc.* 1956, **14**, xiv.
9. Reizenstein, P., Nyberg, W. Paper submitted to the 26th Scandinavian Congress of Internal Medicine, Helsinki, on April 24, 1958. (*Nord. Med.*: in the press.)



Fractionation of liver homogenate by ammonium sulphate and alcohol precipitation. Most of the radiovitamin B_{12} is found in the protein fraction.

absorbed. This may indicate that vitamin B_{12} in the form in which it occurs in liver is absorbed more easily than crystalline B_{12}.

Preliminary studies were made of the B_{12}-binder in pig liver. Liver homogenates were fractionated by precipitation with ammonium sulphate and ethyl alcohol (see figure). Further dialysis experiments did not reveal any significant increase in dialysability after treatment with cyanide or after autodigestion or boiling, whereas both chymotrypsin, trypsin, and acid digestion seemed to permit radioactivity to pass the dialysis membrane.

Autoradiograms and bioautograms of paper strips subjected to electrophoresis (barbitone buffer, pH 8·6, μ 0·05) suggest low electrophoretic mobility of both labelled and non-labelled B_{12}. Ultracentrifugation [10] seems to indicate a larger part of the B_{12} in the nuclei than was previously suspected.[11] Further studies of B_{12}-binders in different tissues and in bile are in progress.

Certainly it is not yet justified to assume that the facilitation of B_{12} absorption is due solely to the vitamin B_{12}-binding substance. Changes in the cobalamin molecule or its stability, in the intestinal wall, or in the speed of intestinal passage, could explain the findings. Also, the differences in dose have to be considered. If, however, absorption is enhanced by proteins or peptides binding vitamin B_{12}, this could eventually furnish information on the functioning of intrinsic factor.

Central Hospital, Vasa, Finland — W. NYBERG M.D.

Medical Clinic and Gustaf V Research Institute, Karolinska Sjukhuset, Stockholm — P. REIZENSTEIN M.D.

10. Hedbom, A., Reizenstein, P. Unpublished observations.

11. Swendseid, M. E., Bethell, F. H., Ackerman, W. W. *J. biol. Chem.* 1951, **190**, 2.

Medical Societies

ASSOCIATION OF CLINICAL PATHOLOGISTS

THE 61st meeting of the Association, held in London on Oct. 2–4, included a symposium on The Cell to mark the centenary of the publication of Virchow's *Cellular Pathology*. This symposium will be published in the November issue of the *Journal of Clinical Pathology*. Some of the other papers contributed to the meeting are briefly summarised here.

Congenital Pulmonary Lymphangiectasis

Dr. K. M. LAURENCE said that congenital pulmonary lymphangiectasis is characterised by progressive, unrelieved cyanosis which generally leads to death within twenty-four hours of birth. At necropsy the bulky and inelastic lungs, with an exaggerated lobular pattern, prominent subpleural lymphatic vessels, and cysts, are diffusely honeycombed with fluid-filled cysts measuring up to 4 mm. in diameter. Histologically these endothelium-lined cysts are situated in abundant young connective tissue under the pleura, and the interlobular septi show a close relationship to blood-vessels and bronchi. The lung parenchyma itself is mature. The position and structure of these cysts, which are shown by reconstructed serial sections to be part of an intricate network of irregular intercommunicating channels, indicate that they are lymphatic in origin.

Familial Pulmonary Hypertension

Dr. J. TREGILLUS (Darlington) and Dr. P. N. COLEMAN (Northallerton) described three fatal cases of primary pulmonary hypertension in a brother and two sisters.[1] In the pulmonary arteries there was extensive intimal proliferation which in the smallest branches had caused serious occlusion. Probably all the intimal proliferation was the result of previous thrombosis. The hypertension was almost certainly genetic in origin. The hypertension was ascribed to an inherited functional defect causing hypertonia in the muscular arteries. Symptomless functional hypertension may have been present for many years, finally bringing about changes in the pulmonary arteries favourable to the development of thrombosis and intimal fibrosis.

Infantile Cardiomegaly

Dr. R. I. K. ELLIOTT said that the infantile form of endocardial fibroelastosis is distinguished by generalised hypertrophy of the heart with dilatation of the left ventricle and thickening of the mural endocardium. Affected children are, typically, apparently healthy until their terminal illness; this may take the form of progressive congestive failure, but more commonly takes the form of abrupt, catastrophic collapse and death in the course of a mild febrile upset. The defect is probably in the myocardium.[2] The condition appears to be familial.

1. Coleman, P. N., Edmunds, A. W. B., Tregillus, J. *Brit. Heart J.* (in the press).
2. Brigden, W. *Lancet*, 1957, ii, 1179, 1243.

Endogenous Lipid Pneumonia

Dr. T. J. MORAN (Pittsburgh) said that in rabbits given intratracheal injections of 1·0% nitric acid, cortisone prevented or modified the resulting bronchiolitis obliterans but did not influence the death-rate from acute pulmonary œdema or pneumonia. In this study a peculiar form of "endogenous lipid pneumonia" was observed in cortisone-treated animals which had been given intratracheal nitric acid. The lipid material in this "endogenous lipid pneumonia" varied greatly in size and was chiefly extracellular.

Nephritis Associated with Streptococcus Pyogenes Type 12

Dr. D. J. H. PAYNE and Dr. D. A. SLADE gave an account of an epidemic of nephritis in North Yorkshire. 5 cases occurred in a small village in the first two months of 1957. Throat and nasal swabs from the local schools showed that infection with *Streptococcus pyogenes* type 12 was highly prevalent in these schools. In all, 43 children, 10 of whom had type-12 strains in their throats, had evidence of kidney damage. Sixteen months later, 7 of the 43 still have abnormal urinary findings—5 with albumin, 1 with red cells and casts, and 1 with red cells only. No more cases occurred until December, 1957. Between then and September, 1958, cases occurred in the Northallerton area and York mainly in the January–March period, as before. 24 cases from the Northallerton area yielded 10 type-12 strains, and in York 9 type-12 strains were isolated from 25 cases and type 22 from another. In all more than 60 cases of acute nephritis have occurred in the area.

Control of Cross-infection by Formaldehyde Disinfection of Blankets

Dr. H. CAPLAN said that regular sterilisation of blankets and bedside curtains is an essential measure in the prevention of cross-infection. Formaldehyde has a direct bactericidal activity which is enhanced by moderate heat and by a vacuum. Using a commercially available formaldehyde generator attached to the ordinary hospital autoclave, blankets are sterilised by exposure to formaldehyde vapour in a vacuum of 15 in. Hg at 55–60°C for twenty minutes. Hot air is then blown through to remove the smell. Up to 50 blankets can be sterilised at a time in an autoclave chamber, capacity 120 c. ft. Following the introduction of this technique cross-infection in a male general surgical ward of 25 beds was eliminated. There was 1 wound infection in the ensuing six months, compared with 17 in the preceding six months. The incidence and severity of urinary infections following prostatectomy were much diminished (from 70–100% to 20%), and the average stay in hospital after prostatectomy was reduced from sixty to twenty days. The consequent saving on drugs alone meant that the apparatus "paid for itself" in less than six months. Blankets have now been sterilised fortnightly for over a year, and have not shrunk or become matted; and formalin dermatitis has not been experienced.

Disordered Indole Metabolism

Dr. M. SANDLER said that assay of biological fluids for indoles by paper chromatographic techniques can only be, at best, roughly quantitative. Qualitative studies, using two-dimensional techniques especially, are of greater value in clinical practice. Diagnostic patterns may be obtained in the carcinoid syndrome, Hartnup disease, phenylketonuria, melanogenuria, and other disorders.

Fractionation of Serum-proteins by Ion-exchange Chromatography

Dr. M. P. TOMBS, Prof. N. F. MACLAGAN, and Dr. K. G. COOKE said that Peterson and Sober had developed a method for the fractionation of serum-proteins into five groups (P, A, B, G, and L in order of elution) on carboxy-methyl cellulose columns. Group P contained mainly α_1 globulins. Albumin was fractionated between groups A and B, but it was shown by re-chromatography that the two forms of albumin were completely interconvertible. They may be related to the electrophoretically distinguishable isomeric forms of albumin reported recently.

α_2 globulins were distributed throughout the elution system. β globulins occurred mainly in group B, and γ globulins in B and G. The areas of the peaks bore a strict quantitative relationship to the amount of protein eluted, and can be used for comparative purposes provided due allowance is made for the different specific absorption of the various components at 280 mμ. It seems that resolution into electrophoretically homogenous components is very unlikely using a single-run technique, but that re-chromatography of groups obtained in a rough elution system such as this one leads to very high resolution. There is no upper limit to the amount of serum which can be employed.

Blood-serum Test for Leukæmia and Neoplasia

Dr. D. STARK MURRAY and J. M. DALY (Kingston-on-Thames) have developed a theory of the mechanism involved in leukæmia which postulates a flaw in desoxyribose nucleic acid (D.N.A.) production in the bone-marrow through a histidine or imidazole compound. This would have the double action of removing zinc ions which normally inhibit D.N.A.-ase and of acting directly as an accelerator of D.N.A.-ase activity. A search for this substance revealed a compound, probably a conjugate since it can be detected only after hydrolysis in a hot alkaline solution (0·5 ml. serum boiled for 30 seconds in 1·0 ml. 20% Na_2CO_3), which appears to be present in excess in neoplastic cases. It is measured by adding 2·5 ml. of diazo reagent and reading with an Ilford filter 404 in the colorimeter against a blank prepared at the same time. No false negatives have been obtained, and only 2 proven false positives out of 346 tests. The test appears very reliable as a diagnostic aid. The normal range is very narrow and distinct from the abnormal. Highest "neoplastic" readings are found in myelogenous leukæmia; in lymphatic leukæmia these are not so high. In carcinoma the figure is always above normal but very variable although all carcinomas give a positive reading. It is possible that some other forms of malignancy do not give positive results, but sufficient cases have not yet been tested. The test is upset by raised urea figures; and false positives are probably related to liver damage. The test may prove to have a value in assessing the effect of different forms of treatment of the neoplastic diseases.

Reviews of Books

The Borderland of Embryology and Pathology

RUPERT A. WILLIS, D.SC., M.D., F.R.C.P., emeritus professor of pathology, University of Leeds. London: Butterworth. 1958. Pp. 660. 90*s*.

IT is clear that Professor Willis, in writing his justly successful *Pathology of Tumours*, had to avoid (lest that work become unmanageable) a great number of borderline topics which he found intensely interesting. He has gathered many of them into this book. Though the theme of the title is successfully used to bind together much of the contents into a logical order, the thread is lost just after the halfway mark, and the result is something of a mixed bag: but only purists will complain, for the effect is to allow the inclusion of all manner of topics which less eclectic works have no place for.

The book begins with a useful summary of human embryology, though, apart from some of the histology, most of it is already accessible. The core of the book follows, with an account of malformations, hamartomata, and the like, somewhat arbitrary in its inclusions and exclusions (congenital heart-disease, for instance, is dismissed very briefly). The following random sample (collected by the "Sortes" method) indicates the ground covered: twinning; ætiology of fœtal abnormalities; odontomes; tuberous sclerosis; juxta-gonadal vestiges; angiomata; intestinal polyposis. Thereafter there are sections on inborn metabolic disorders (too synoptical perhaps), on embryonic tumours and teratomas, on fœtal diseases, on repair and regeneration, on metaplasia (a long and specially valuable chapter), and on tissue transplantation.

As is to be expected from our Rupert of pathological debate, dogmatism, verging sometimes on intolerance, is often evident. Yet he marshals his facts and references with such clarity and honesty that even those who disagree with his conclusions must be grateful for his continuous illumination of the subject. "Proving Willis wrong" on minor points is a major occupation of young pathologists all over the world—a tribute to a thoroughness and lucidity which everywhere serves to define the nature of problems, even when the answer suggested is not the best possible. The book is a "must" for pathologists, and there is much in it for almost every kind of doctor.

Renal Circulation in Acute Renal Failure

OLE MUNCK, M.D., physician, Rigshospitalet, Copenhagen. Oxford: Blackwell Scientific Publications. 1958. Pp. 54. 12*s*. 6*d*.

THIS monograph describes methods for measuring renal blood-flow by the uptake of radioactive krypton, and intra-renal pressure by catheter wedged in the tributaries of the renal vein. Six patients with acute renal failure were found to have a relative renal blood-flow about a third that of normal subjects, in contrast to the much lower results based on clearance of *p*-aminohippurate. The intrarenal pressure in five patients with acute renal failure was normal. The bearing of these important findings on the pathology of acute renal failure is discussed.

Cholesterol

Chemistry, Biochemistry and Pathology. Editor: ROBERT P. COOK, M.B., D.SC., University of St. Andrews, Queen's College, Dundee. New York and London: Academic Press. 1958. Pp. 542. £5 7*s*. 6*d*.

CHOLESTEROL is widely distributed in the animal kingdom and well merits a monograph in its own right. The now established fact that coronary-artery disease is associated with a disturbance in the metabolism of cholesterol adds further interest to this book. Dr. Cook has assembled a strong team of American and European scientists and they have produced a book packed with useful information and references and invaluable for research teams working on atheroma and related problems. Doctors will find an excellent account of the physiology of the circulating cholesterol and lipoproteins by Boyd and Oliver—the most lucid summary of recent work yet prepared. They will also appreciate the chapter on the metabolism of cholesterol by Gould and Cook. Much of the rest of the book they will find hard going: in particular, the chapter, 90 pages long, on the chemistry of cholesterol makes no allowances for basic ignorances.

Our understanding of the functions of cholesterol in the animal organism is growing rapidly, and there will be a need for a second edition before many years are out. Dr. Cook might then consider whether he would not produce a better book, coherent in style and easier to read, if he wrote it all himself or with the aid of only one or two colleagues.

THE LANCET

LONDON 18 OCTOBER 1958

Separatism or Reintegration?

"THE need of these times", we said six years ago, "is to begin to reintegrate the various branches of medicine, and we do not believe that the best interests of the profession will be served by separatist movements that may presently fill the medical scene with quite a number of new colleges—not only of general practitioners, but also of pathologists, pædiatricians, psychiatrists, and others." [1] The function of a college, as we saw it, is something far bigger than to represent a group of people who practise the same specialty: it is to promote the growth of medical art and science over an area that nowadays covers many specialties. We argued that the three Royal Colleges in London were in process of becoming colleges of medicine, surgery, and obstetrics, rather than closed corporations of physicians, surgeons, and obstetricians. We pointed to the developments that have made the College of Surgeons the centre of a group of affiliated faculties, and the College of Physicians "a remarkably catholic assembly, comprising almost every kind of doctor except (at present) general practitioners". But appreciation of these fundamental changes, and of their implications, is still hindered by the fact that the senior colleges have names given them in distant days when there were only three specialties. Because in Britain the word "physician" is now generally limited to a particular kind of clinical consultant, the College of Physicians is regarded by many outsiders as simply the representative organ of this group. Indeed there are times when the college itself, hypnotised by its title, seems to take the same narrow view of its functions. Yet if it rejects its integrating role as a College of Medicine, it will inevitably promote separatism, and thus reduce both its usefulness and its influence. If internists claim a college of their own, they can scarcely object if each of the other vocational groups demands a college too. (The contribution of some of them to medicine is no less important than the internists'; and in twenty years' time it may be more important.) That the prestige of existing colleges must diminish with each addition to their number may not matter if the gains are proportionate; but we cannot think they will be.

Each specialty, large or small, should have its vocational representative body—a faculty perhaps,[2] or an association. But each specialty should also have access to a college—an academic body of wider scope. In pathology, allegiances and opinions have been divided; but Dr. MCMENEMEY's impressive presidential address to the Association of Clinical Pathologists (p. 841) sounds like a final plea to the College of Physicians to give pathologists the academic home which there or elsewhere they must find. Not only does pathology stem from a clinical tradition but the pathologist of the future will remain, he believes, a doctor rather than a technologist. Meanwhile, today, the pathologist's clinical responsibility is high, and his "zeal for technical efficiency . . . should be no excuse for abandoning that postgraduate training in clinical medicine which all consultants need to acquire". Because a knowledge of general medicine is of more value to pathologists than an acquaintance with anatomy or proficiency in surgical technique, their adherence "is primarily to the Royal College of Physicians": the pathologist is indeed a kind of physician. But all too often pathologists are denied admission to the physicians' college because they have been working more at the bench than at the bedside. An entrance examination with a pass-rate of about 12% is formidable to anybody, but in the present membership examination the emphasis is so strongly clinical that few candidates can hope for success unless they have concentrated for some time on purely clinical practice. Hence its particular difficulty for pathologists. "It is often in fact more than a difficulty, it is a deterrent." Though young pathologists are commonly recommended to seek the membership, many refrain from doing so because the examination, as now arranged, is a disturbance to their education rather than an appropriate part of it.

MCMENEMEY suggests that, without in any way lowering the high standard of its membership examination, the college should remove the disability it imposes on the prospective pathologist—as might be done, perhaps, if rather lower marks in the clinical tests were acceptable from candidates who are prepared to demonstrate their aptitude for pathology. Though to some clinicians (who properly set great store by the clinical examination) this may seem a subversive proposal, we hope they will refrain from dismissing it out of hand. An argument often put forward is that, since the membership is a hallmark of clinical ability, its conferment on junior pathologists would cause confusion: indeed a pathologist might later secure a clinical post, improperly, on the strength of it. But this argument is really no more than a relic from the days when the M.R.C.P. was regarded as a test of knowledge qualifying its holder for work as a physician. In recent years the college has repeatedly declared that the examination is now, in fact, nothing of the kind: it is meant to be taken two or three years after qualification and its purpose is simply to ascertain whether the candidate is qualified for *training* as a specialist—e.g., in a post as senior registrar. In Britain at least, consultant appointments are not made on the strength of success in any examination (though such success may be one requirement), but mainly on the doctor's performance in his training post and afterwards; and it is inconceivable that anyone—were he M.R.C.P. three times over—would be appointed as a clinical consultant unless he had also proved his clinical ability in many years of hospital practice. With only

1. *Lancet*, 1952, i, 139.
2. *ibid.* 1951, ii, 1071.

minor adjustment, the membership examination could be made an equally satisfactory test of the young doctor's suitability for training as a pathologist. If, having passed this test, he afterwards changed his mind and took up clinical medicine, he would still have to demonstrate his clinical aptitude in competition with his clinical coevals. There would be no greater risk of erroneous selection for a consultant appointment than now exists when a prospective clinician decides to make his career in pathology.

Remarking that in the past "many a physician has been launched on a meteoric career from the ramp of the hospital laboratories", McMENEMEY says all too truly that the National Health Service has facilitated the erection of barriers between the specialties. The urgent desire of the colleges should surely be to break down such barriers, not to make them higher or more permanent. For the Royal College of Physicians a turning-point has been reached at which the choice between separatism and reintegration affects not only pathologists but also its own future.

Crohn's Disease after Twenty-five Years

Now that a quarter of a century has passed since CROHN and his colleagues [1] first described terminal ileitis (later known as regional ileitis, then regional enteritis), what advances have been made? The spectacular in medicine lies in the revelation of specific cure or of cause. With Crohn's disease there has been no such development; indeed the boundaries of its clinical features have become blurred by terminological differences and even by uncertainty regarding its sites of predilection. Though none would dispute that the terminal ileum is the commonest site of the gross lesions, other parts of the alimentary tract, from gullet to anus, can be attacked. Dr. CROHN himself, after reviewing his incomparable personal series of almost 600 cases, considers that the large bowel is attacked very rarely—probably in no more than 5% of cases—unless it has become involved secondarily from contact with diseased ileum, by fistula formation, or after resection.[2] Yet in a British series reported by BROOKE [3] the initial lesions were found to involve the large bowel in about half of 121 cases; and JACKSON [4] reports colon involvement in 31% of 126 cases treated at the Massachusetts General Hospital—though whether this involvement was primary is not stated. JACKSON also refers to a further 14 patients (making 43% in all) in whom ulcerative colitis involved the whole colon at some time after regional enteritis was diagnosed. Unfortunately no specific test, histological or biochemical, distinguishes the one from the other.

Ulcerative colitis proper affects primarily the large bowel, and any involvement of the small bowel usually develops when the ileocæcal valve has become incompetent and is insufficient to result in steatorrhœa (which is present in many cases of Crohn's ileitis). Furthermore, whereas in ulcerative colitis the gut wall is not thickened, in Crohn's disease it is considerably thickened. Fistula, other than anorectal, is extremely rare in ulcerative colitis and usually develops because a pericolic abscess from a localised perforation has burst through into an adjacent viscus (stomach or jejunum, for example); whereas in Crohn's disease fistula formation is fairly common but does not appear to result from such acute crises (perforation is rare [5]), but instead develops gradually from contact with the inflamed intestine. In ulcerative colitis the mucosa between ulcers seldom appears normal, though it often remains so proximal to ulcers in the transverse or descending colon; in Crohn's disease ulcers in the colon appear more discrete because of the apparent normality of the intervening mucosa. Differentiation of the two disorders is important not only for a better understanding of them but also because surgical techniques for ulcerative colitis may be unsuitable for Crohn's disease. In Crohn's disease small-bowel lesions have developed above an ileostomy after proctocolectomy [6]; and one of JACKSON's 14 patients with the "combined" disease died from ileostomy dysfunction.[7] YARNIS et al.[8] have drawn attention to the difficulty in treating combined forms.

The chief advances in Crohn's disease have followed painstaking study of series of cases over years. CROHN has observed that we shall not have a full picture until the disease has been studied throughout a life's span. It commonly affects adolescents, and most patients are expected to live their normal span;[5] so a fair prognosis may be given, though the patient will undoubtedly have to endure corticoids, surgery, and periods of incapacity on the way. Only 85 of 542 patients in CROHN's series escaped operation, and of these the disease was considered to be arrested in 51.[5] Here is an odd paradox: that 80% have been submitted to operation, though surgery is no longer the treatment of choice. The passing of the anatomical era in surgery has damped the desire to cut any abnormality out as soon as it is detected; with regional enteritis the itching fingers are learning to withhold. Surgical minds are now alive to the possibility that invisible defects lie apart from the gross lesion—lurking there to cause overt recurrence another day.

As follow-up studies have been extended to ten and even fifteen years so recurrence-rates of 60–80% have been reported.[9] Extrapolation of these figures would surely give a 100% recurrence-rate in a normal life-span; yet the recent statistics from CROHN show that the rate was 27% in a follow-up period extending from one to twenty-five years.[5] JACKSON, who reports an overall recurrence-rate of 55% and spontaneous remission in only just over 1% in a follow-up of 126 cases over two to twenty years, considers that, despite many examples of recurrence fifteen to twenty years later, a patient who

1. Crohn, B. B., Ginzburg, L., Oppenheimer, G. D. *J. Amer. med. Ass.* 1932, **99**, 1323.
2. Crohn, B. B. Address to British Society of Gastroenterology, November, 1957.
3. Brooke, B. N. See *Lancet*, 1958, i, 1314.
4. Jackson, B. B. *Ann. Surg.* 1958, **148**, 81.
5. Crohn, B. B. *Gastroenterologia*, 1958, **89**, 352.
6. Brooke, B. N. *Ann. R. Coll. Surg. Engl.* 1957, **20**, 114.
7. Jackson, B. B. *Ann. Surg.* 1958, **148**, 88.
8. Yarnis, H., Marshak, R. H., Crohn, B. B. *J. Amer. med. Ass.* 1957, **164**, 7.
9. Van Patter, W. N., Bargen, J. A., Dockerty, M. B., Feldman, W. H., Mayo, C. W., Waugh, J. M. *Gastroenterology*, 1954, **26**, 347. Cooke, W. T. *Ann. R. Coll. Surg. Engl.* 1955, **17**, 137.

has been free of trouble for over four years is likely to remain so. Nevertheless the high rate of recurrence has caused surgeons to abandon attempts at cure and instead to concentrate on "holding" operations—operations to keep the patient going. Accordingly, at the outset remission is obtained by conservative means—notably administration of corticosteroids and vitamin B_{12} and remedying of potassium loss—and operation is withheld until obstruction, fistula, or intractable diarrhœa demand intervention.

Opinion differs regarding the surgical method, for though at Mount Sinai Hospital CROHN opts for bypass by anastomosis and exclusion, since the recurrence-rate is no greater than that following resection while the operative mortality is half (4% compared with 9·6%),[5] elsewhere resection is preferred[10]; and at Boston[4] the operative mortality figures are reversed (7% in 57 short-circuit operations, compared with 4·5% in 86 resections), though the effect of reserving short-circuit for the more difficult case must here be borne in mind. Perhaps after a quarter of a century, though we know the disease better, we understand it less.

Long-term Outcome in Tuberculous Meningitis

IT is now eleven years since streptomycin was first used for the treatment of tuberculous meningitis. Much attention has been given to the use of this drug alone and in conjunction with others, such as isoniazid, *p*-aminosalicylic acid, the corticosteroids, and intrathecal tuberculoprotein. Growing emphasis has been placed on diagnosis and proper treatment early in the disease: the tuberculous process has an aptitude for producing both endarteritis and constrictive exudates round that most eloquent part of the central nervous system, the midbrain,[11] and it is essential to arrest its progress before function is irreversibly impaired.

Nowadays a two-year survival-rate of less than 80% suggests that the treatment was at fault, and of the survivors very few should have residual disability other than loss of vestibular function. But what of the long-term follow-up? There are no really adequate published accounts from any of the recognised treatment centres, although recent papers[12 13] have given important information in a condensed form. There are three broad considerations here: (1) the effects of irreversible neurological damage sustained during the acute illness; (2) the incidence of late relapse; and (3) the delayed onset of disorders produced either by organisation of or by enlargement of residual tuberculous lesions.

Irreversible damage is generally agreed to arise most commonly in patients in whom the disease is advanced at the start of treatment. Hemiplegia, optic atrophy, and dementia are almost certainly due to the disease itself; whereas deafness and cauda-equina lesions (the latter fortunately rare) are probably iatrogenic, the former being due to streptomycin and the latter to traumatic spinal puncture. Published accounts are most heartening in suggesting that even severe disability has not prevented full-time employment of treated adults, and that the majority of children do not subsequently show much mental or physical disability. Publication of detailed studies of these points would be welcome.

By analogy with tuberculous disease in other organs, foci of viable organisms might survive in a quiescent state for many years before giving rise once more to active, widespread disease. The reported incidence of such late relapses—as opposed to those within months after treatment has been stopped—is surprisingly low. In the Oxford series[14] no patient among those treated there from the outset has relapsed after treatment and full convalescence; and LORBER[12 15] reports only 7 clear-cut relapses between one and eight years after the first attack. Delayed neurological and endocrinological complications are also rare. Focal epilepsy[16] and diabetes insipidus and sexual disturbances[15] have been reported. The infrequency of the last two is surprising in view of the propensity of the tuberculous process for forming exudate in the basal cisterns and round the brain-stem. It is also remarkable that cord lesions are so infrequent. The high incidence of paraplegia reported by BROOKS et al.[17] is unusual, although postmortem examination of the spinal cord after death at the height of the illness shows an astonishing amount of exudate in the meninges compressing the cord, especially when a spinal block is present.

In contrast to the low incidence of relapse and other late complications is the high incidence of intracranial calcification after treatment, reported notably by LORBER[12 18] and ACHESON and SMITH[13] in their radiographic studies. LORBER showed that in 68% of children detectable calcification had developed two and a half years or more after treatment; and the findings of ACHESON and SMITH essentially agree with his. Calcification is commoner in children than adults, and in patients whose treatment was not started until the disease was advanced. It is commonest in the basal meninges and may thus be correlated with the most important site of exudate in the active infection. The incidence is a little higher in patients with neurological sequelæ than in others. Both LORBER and the Oxford workers have investigated radiographically an impression gained from postmortem study that intrathecal tuberculin helps to resolve tuberculous exudate. Their observations on intracranial calcification suggest that this impression is correct; but the numbers were insufficient for a firm conclusion. It seems that only a long-term follow-up will show whether there is any relation between the exact form of treatment, the incidence of intracranial calcification, and the ultimate prognosis.

10. See *Lancet*, 1958, *i*, 1315.
11. Smith, H. V., Daniel, P. *Tubercle, Lond.* 1947, **28**, 64.
12. Lorber, J. *Amer. Rev. Tuberc.* 1958, **78**, 38.
13. Acheson, R. M., Smith, H. V. *Quart. J. Med.* 1958, **27**, 83.
14. Smith, H. V., Vollum, R. L., Taylor, L. M., Taylor, K. B. *Tubercle, Lond.* 1956, **37**, 301.
15. Lorber, J. *Arch. Dis. Childh.* 1958, **33**, 315.
16. Lorber, J. *Proc. R. Soc. Med.* 1951, **44**, 916.
17. Brooks, W. D. W., Fletcher, A. P., Wilson, R. R. *Quart. J. Med.* 1954, **23**, 275.
18. Lorber, J. *Arch. Dis. Childh.* 1952, **27**, 542.

Annotations

THE TRIUMVIRATE OF HEREDITY

In this year of the centenary of Darwin's famous paper to the Linnæan Society it is natural that the impact of his recognition of natural selection as the force behind evolution should be recalled with appreciation and respect. But, as Prof. Robert Platt justly pointed out in an address to the Osler Club on Oct. 8 (and as Darwin, with his innate generosity and modesty, would today have doubtless agreed), his contribution to biology was reinforced and extended by two other remarkable men.

Though Darwin realised that the variations which Nature selected are passed on by a hereditary process, to the end of his life he had no idea how that process worked. The laws that governed it were first demonstrated by Johann Mendel, who was born thirteen years after Darwin in a remote Silesian village. In background and upbringing the two men were dissimilar. Darwin came of a prosperous professional family, many of whose members had shown unusual gifts. Mendel was a lone genius born to a family of poor peasants who at great sacrifice to themselves managed to provide him with education at local schools and colleges. Like Darwin, however, Mendel felt the need to retreat from the cramping difficulties of everyday life. Instead of the support and shelter of a private income, the shawl and couch of semi-invalidism, and the solicitous care of a wife, he found the way of life he needed in monasticism. In 1843 he was received into the Augustinian monastery at Altbrünn. Like Darwin, he seemed to have been happy and successful in his choice, and in 1868 he was elected abbot of his monastery. Like Darwin, too, he presented his seminal work to the world in a paper to a learned body. But instead of the Linnæan Society, he not unnaturally chose as his forum the Naturforschender Verein in Brünn. His work differed from Darwin's in that it was not a theory based on long and exhaustive observations, but an exact mathematical formula based on eight years of deliberate, planned, limited, and elegant experiments with 34 varieties of peas.

The third member of the triumvirate, Francis Galton, had much more in common with Darwin and was indeed his first cousin. He shared with him many of the genes which Mendel had discovered, a more than comfortable private income, English university education, years of travel abroad, and a convenient amount of ill health. His interests and his inventive mind ranged widely. He designed a whistle with a high note perceptible only to dogs, meteorological maps, a wave machine to work ships, and a bicycle speedometer, and he was the first to suggest how finger-prints could be used for identification. The publication of the *Origin of Species* was a crisis in his life, and he began to collect statistical evidence from families to show that intellectual as well as physical qualities are inherited. His human material could not be subjected to the exact discipline of Mendel's peas and bees, but so far as he could he applied statistics to biology, and he early realised the importance of twins in the study of genetics. His work convinced him of the value of eugenics for the human race, but he recognised the need for the collection of more data before its principles could be implemented.

The contrast in the way in which the work of these men was received is to us ironical. As Professor Platt pointed out, Darwin's, which showed that evolution depended on the survival of the fittest, was hotly debated everywhere and antagonised nearly every bishop who read it; while Mendel's, which showed that the laws of heredity are the laws of chance, passed unnoticed, though it emanated from a monastery. The work of both men was slow to influence medicine—perhaps, Professor Platt suggested, because in a society whose major ills were poverty, squalor, and infection environment not unnaturally seemed to be a more urgent problem than heredity and evolution. But now that these difficulties and dangers are so nearly overcome in Britain, and constitutional disorders—such as arterial degeneration, high blood-pressure, and cancer—are the chief causes of death he believes that the doctor may with profit turn to a closer study of the interaction of heredity, natural selection, and environment.

URGENT ADMISSIONS

When a hospital is already just about full, applications for immediate admission are apt to cause acrimony at both ends of the family doctor's telephone line. The G.P. may waste time and temper trying to locate admitting officers; the hospital may grumble at overwork and inadequate or inaccurate case-histories. An experienced G.P. may dislike having to justify his diagnosis to a houseman, and having to recite pulse and respiration rates; the houseman dislikes handing over his last bed to an elderly patient from the other side of town who ought to be looked after nearer home. To help to smooth out some of these difficulties emergency bed services and bed bureaus have been started in many parts of the country, and changing population and lagging hospital building have made them essential, especially in winter.

To clear up some common misconceptions about the work of these services Dr. Clifford Ellingworth [1] has investigated 1297 requests to the Emergency Bed Service for admission to thirty London hospitals. As a past medical superintendent and a present medical officer of the E.B.S., he has, as it were, sat at both ends of the telephone, and he found that 1241 of the requests were justified, 43 patients had been grossly misdiagnosed, and another 13 had been sent home from the hospital as not requiring admission. Even hospitals are not always right, and it is perhaps a pity that Dr. Ellingworth did not ask the G.P.s for their reactions to the return of these patients. It seems clear, however, that the service is little misused, and the figures are a tribute to London doctors. On the other hand, he feels that it could sometimes be better used. For instance, some G.P.s fail to telephone the local hospital before turning to the E.B.S., because of the time that can be wasted on such a call. This attitude would probably change if all hospitals had an efficient call-system, for there are still hospitals where porters are dispatched on melancholy half-mile walks round all the places the internal telephone does not reach. Calls are most efficiently handled where there is a central point of day and night duty, such as a casualty department.

Dr. Ellingworth believes that there is probably some truth in the reproach that some doctors send their interesting cases to their local hospital and the others to the E.B.S. Another complaint that is not without substance is that some patients are already moribund when they are sent to hospital. But what is the family doctor to do when gross overcrowding makes it impossible for the patient to die at home? Dr. Ellingworth suggests that teaching hospitals could help more by taking back their former patients in an emergency. As it is, the area hospital may have to begin investigations again from scratch. In winter respiratory infections account for nearly half the cases

1. Ellingworth, E. *Hospital*, August, 1958, p. 577.

handled by the E.B.S., though the new antibiotics might be expected to allow more patients to be treated at home. Dr. Ellingworth agrees that patients should if possible be treated near their homes; but, since beds are distributed unevenly, the load must be spread and hospitals must avoid "area consciousness".

Disquieting difficulties are also being met in dealing with maternity cases. These rose from 950 in 1955 to 1600 last year. The E.B.S. believes [2] that the bed shortage leads some antenatal clinics to advise patients to call their doctor when labour starts, and ask him to arrange admission through the service. This unsatisfactory procedure has led to anxiety and inconvenience, and to babies being born in unsuitable places. As the report of the service points out, this last-minute rush to obtain an "emergency" bed for a patient who should never have become an emergency cannot but have an unfortunate effect on the mother.

But the biggest problem is of course to find beds for the elderly and infirm. Until more homes and half-way homes are provided for them the acute wards of our hospitals will have to continue to carry, albeit reluctantly, the overflow of social problems. The community might be better served if the needs of the old and the young were reassessed more realistically. As it is, the treatment of the young and acutely ill is satisfying and highly valued in society at large, whereas the treatment of the old and chronic is less highly valued; so units tend to hoard beds for the young and management committees to keep on some acute wards that are half-empty in summer. Rational planning of beds and services and the integration of geriatrics into the general hospital would help to solve some problems (especially of nursing) and go a short way towards countering the bed shortage. Domiciliary treatment has certainly an expanding future; and it is desirable that old people, whenever possible, should be treated in familiar surroundings. But from a practical point of view, especially in these broad-spectrum days, it is more often the young that can be managed at home.

ELECTROCARDIOGRAMS BY TELEPHONE

TRANSMISSION of the electrocardiogram by special wiring from the bedside to the cardiac department was widely used when the instruments were large and unwieldy, and Einthoven himself operated the unit in his laboratory with the patient in the ward in Leyden as early as 1905. A connection over a distance of nearly a mile was made in 1916 between the university pathological laboratories and Addenbrooke's Hospital in Cambridge. The advent of alternating current caused troublesome interference in the transmission lines; and in any event the system was clumsy, requiring expensive installations, two technicians, and a system of communication between them. It went out of use in most hospitals with the introduction of portable cardiographs.

In America publicity has recently been given to a small portable modulator weighing 5 lb. which can transmit the electrocardiogram or heart sounds through the telephone system merely by placing the instrument near the telephone mouthpiece. [3] At any moment the signal can be interrupted and the telephone used for communication between the operators at each end. At the receiving end a receiver demodulates the signals, which are then fed into any type of electrocardiograph.

The system sounds attractive and might be useful in occasional emergencies; but it requires two operators and is hardly likely to come into routine use now that small, light, transistorised, direct-writing electrocardiographs are obtainable. There is, however, no limit to the distances over which the signals can be sent, as was recently shown by their transmission from Bethesda, Maryland, to Kansas City more than 1000 miles away. It was suggested that this method might be useful in "space medicine" for keeping a check on a person in a satellite.

EVOLUTION AND ENURESIS

Harper [1] has lately presented evidence for believing that phlebothrombosis may arise from the survival of primitive mechanisms whereby a frightened animal prepared for fight and injury by shortening its blood-clotting time. He has also given some grounds for believing that outmoded defensive mechanisms may be involved in peptic ulceration, and he refers to the possibility of diabetes, allergies, and neoplasia being similarly derived. Prof. John Bostock, of the University of Queensland, has been thinking independently along similar lines. His earliest studies were on enuresis and he has recently brought his work up to date.[2]

He suggests that, in the light of the evolutionary theory, the gestation of the child is to be regarded as "interior" (the usual nine months) and "exterior". The period of "exterior" gestation he puts at eight to ten months and ends when the sleep pattern of the child changes—i.e., sleep becomes elective—and the child is capable of some independent locomotion. The limitations of the pelvic outlet have, he says, obliged Nature to split the early phase in this way and have made the newborn child the helpless creature it is. The sleep of the neonate is quite different in time and profundity from that of the adult, and Bostock thinks that the majority of nocturnal enuretics suffer from persistence of this deep primitive sleep into later life. His studies of enuretic children free from organic disease (90% of cases) showed that they responded much less to certain standard stimuli than did others; and when at length they were awakened, their actions had an automatic quality. After long inquiry into the training techniques of mothers, he concluded that the reason for this persistence of the primitive pattern was consistent early preoccupation with toilet training. The baby wakes only to be fed, and any "artificial" wakefulness after this for playing or potting is paid for by deeper sleep and, says Bostock, a sleep disturbance in later infancy. He has investigated over 200 enuretics (with controls), and this finding has been consistent to a high degree of significance. In explanation of the "solitary enuretic" in a family of other children, he cites numerous instances where that child, for one reason or another, received different treatment in this respect from the others. The primitive community, he explains, understands the primitive child much better. Mother usually swaddles it tightly, feeds on demand, and leaves it very much alone as far as entertainment and hygiene are concerned: it might even be sewn up in its bindings for months at a stretch. Such customs must not be lightly disregarded, based as they are upon many hundreds of years' experience and experiment. The much-scrubbed and powdered baby of today is, according to Bostock, quite a recent innovation.

Examining the personality and background of each of

2. Annual Report of King Edward's Hospital Fund for London for 1957, p. 24.
3. Dimond, E. G. *J. Amer. med. Ass.* 1958, **167**, 1624.

1. Harper, R. M. J. *Lancet*, July 12, 1958, p. 92.
2. *Med. J. Aust.* 1958, ii, 149, 185.

20 mothers of enuretics, Bostock found that 17 had enjoyed excellent relations with their own mothers, had identified with and accepted the feminine role completely, and had in turn enjoyed their own motherhood. They were excellent mothers whose error had lain in the excess of attention lavished on the baby. In the other cases there were social or other reasons why attention to the infant had been excessive. 15 mothers had obsessive-compulsive tendencies. The persistence of psychological patterns in this way from generation to generation could well account for the familial aspect of enuresis,[3] although Bostock believes there is a true genetic type due to delayed maturation: he adds that further study is likely to reveal other enuresis syndromes. Pants-wetting, he says, is a different condition; and unfortunately he does not try to explain the "acquired" form of enuresis in which control is first gained and then lost. This group is said by Hallgren [4] to account for 15% of cases.

Professor Bostock has made out an excellent case. His theory has much in common with that of Cruden,[5] who held that sleep is the natural state of man and that consciousness comes gradually through the development of "wake-maintainers". Are drowsy people primitive and insomnic ones highly advanced? Bostock has also worked on asthma and concluded that this disorder too arises from primitive mechanisms—in this case of crying and speech.[6] This also, he judges, is connected with early mismanagement; but here the theoretical background seems less convincing and less open to confirmation by experiment.

PICKING THE WINNERS

As every doctor knows, prognosis is a risky business. Like all judgments relating to human beings, our forecast of the outcome of a physical illness in a single patient may be wildly astray. When we attempt to compare the probable mental abilities of a whole group of people at an unspecified time in the future we are clearly faced with a far more difficult task. Yet this is what is expected of every university selection committee and every committee awarding research grants to junior graduates.

Much effort has been spent in trying to reduce wastage associated with academic failure during undergraduate courses. School records, intelligence tests, personality assessments, and aptitude tests have all been correlated with scholastic performance in the university course, and the results of first-year examinations have been compared with those in later years. These investigations have for the moment petered out into generalities, for no satisfactory objective basis for prediction has yet been found.

Less attention has been paid to the allied problem of selecting research-workers from recent graduates, though this is of immense importance. "Today, when the very existence of modern society depends upon the continued advancement of knowledge, we can no longer afford to rely upon the unassisted emergence of the rare genius. We must discover and develop the mass of latent talent that exists." [7] But how are we to do this? A capacity for passing university examinations is not necessarily linked with a talent for making original observations and synthesising them into new discoveries; and relatively few students have much opportunity for original work as undergraduates. Nevertheless, there is a very general impression that research ability is bred by academic success, and "selection will largely be based upon the quality of their academic careers and the assessment by their teachers".[8]

Gross and Hudson [9] have begun an investigation into the validity of this practice. Taking admission to the fellowship of the Royal Society as their criterion of research ability, they prepared a list of those current fellows who received their first degree from Oxford or Cambridge, and then examined the published class of degree which they obtained. They find that "approximately 1 in 4 of the group who graduated from Cambridge during the period 1920–39 gained a second or third in their final examination, and that approximately 1 in 3 gained a second or third at some time during their undergraduate careers". The Oxford fellows graduating in the corresponding period appeared to have a better record than their Cambridge counterparts, there being only 1 "second" in 31 results, and no "thirds" at all. This discrepancy between Oxford and the Other Place is, as Gross and Hudson point out, open to two interpretations according to the direction in which one's sympathies are engaged: either the Oxford examination is a more valid index of potential research ability than is the Cambridge one, or else—oh horror!—the standards of the Oxford examinations are lower than they are at Cambridge.

This investigation is naturally incomplete; and further work is in progress to extend its scope beyond Oxford and Cambridge, and also to select other criteria of research ability, such as the obtaining of a D.SC. But the main point appears to admit of little argument: it would be foolhardy to base predictions of future research performance solely on academic success, even at the end of an undergraduate career. As in preselection for the university, there is no wholly trustworthy objective basis for preferring one candidate to another, and we are thrown back on the purely subjective human judgments which have had to suffice for this and similar problems since the dawn of history. There is still room for opinions, based on experience and tempered with humility, in the ordering of scientific affairs.

B.M.A. CLINICAL MEETING

THE annual scientific meeting of the British Medical Association is traditionally held during the annual gathering of the Association in July. The Association has now arranged to hold a second scientific meeting during the winter months in a town which could not reasonably undertake to act as host to a full annual meeting. The first of these annual clinical meetings, as they are to be called, will be held at Southampton from Dec. 4 to 7. Prof. A. P. Thomson, president of the Association, will open the meeting, and during the first afternoon session there will be a Transatlantic clinical conference, by telephone, with the American Medical Association's meeting at Minneapolis. Clinical demonstrations will be held at the Southampton General Hospital, the Royal South Hants Hospital, the Southampton Eye Hospital, and the Southampton Chest Hospital.

Mr. GEORGE SEED, aural surgeon to the Leeds General Infirmary, died on Oct. 11 at the age of 53.

3. See *Lancet*, 1958, i, 576.
4. Hallgren, B. *Acta psychiat., Kbh.* 1957, **32**, suppl. 114.
5. Cruden, W. V. *Lancet*, 1957, i, 579.
6. *J. ment. Sci.* 1956, **102**, 559.
7. The Support of Medical Research (edited by H. Himsworth and J. F. Delafresnaye); p. 7. Oxford, 1956.
8. *ibid.* p. 35.
9. Gross, C., Hudson, L. *Nature, Lond.* 1958, **182**, 787.

Special Articles

THE FUTURE POSITION OF THE PATHOLOGIST IN MEDICINE *

W. H. McMENEMEY
M.A., D.M. Oxon., F.R.C.P., D.P.M.
PATHOLOGIST TO THE MAIDA VALE HOSPITAL FOR NERVOUS DISEASES, LONDON, W.9

WHEN in the year 1215 Pope Innocent III decreed against the practice of medicine and surgery by ecclesiastics (*Ecclesia abhorret a sanguina*) the Christian medical profession was born. Soon after this we find pathologists at work in the persons of William of Saliceto (1201–80) and Taddeo Alderotto (c. 1223–1303) both of Bologna. Since their day, clinical medicine and pathology have kept in step, and the practice of the one has been identified with that of the other, until within our lifetime.

DEVELOPMENT OF PATHOLOGY IN ENGLAND

Pathology was slow to develop in England—perhaps because of the rarity of the microscope, or more likely because there was virtually no corporate life within the profession. The Royal Society and the Royal Institution were almost alone in providing a forum for the medical scientists. Medical journalism was then still in its infancy and ineffective.

Eight years after Wellington's victory at Waterloo and at a time when the medical world still read Bichat and Corvisart, and awaited with interest the publications of Laennec and Cruveilhier, one critic commented on the lamentably poor state of pathology in this country, saying "we have scarcely any works which treat on general pathology—none original on anatomy—we could not recommend a small English book to be translated into French when asked".[1] It was not that the outstanding achievements of John Hunter as an experimentalist had been overlooked, but simply that thirty years after his death the profession was not organised.

William Farr [2] in 1837, comparing unfavourably the state of pathology in this country with that in France, blamed an apathetic Government for not realising the association between the progress of medicine and the public welfare. He might equally have blamed the colleges for their nepotism and their restricted outlook.

However, by 1845, partly through the influence of the medical press and partly because of the interest of certain societies, there had grown up a desire to extend and cultivate the knowledge of pathology. We read that "chemical research and the microscope are earnestly devoted to this object" and that "diagnosis is assisted by frequent resort to chemical analysis of the blood and urine". At this time doctors were encouraged to join the recently founded Royal College of Chemistry, and Liebig was predicting that the next great step in the advance of medicine would be made with the aid of organic chemistry. The far-seeing John Simon was quick to recognise the worth of the chemical pathologist, and especially the genius of Thudichum.

Some of our medical societies date from the late 18th century, but the majority were born of that sudden craving for learning that characterised the peaceful but poverty-stricken late 1820s, and they covered the whole field of medicine.

The Reform Act of 1832, and the abortive Bills which preceded it, stimulated a scattered and ill-organised profession to put its house in order so that we find the earliest activities of the Provincial Medical Association (the parent body of the B.M.A.)—laudably designed as a scientific and social body—preoccupied with medical education, poor-law reform, quackery, and medical polity in general. These pressing matters and other internal business kept their annual meetings busy until the passing of the Medical Act in 1858; but, sandwiched in between retrospective addresses and the reports of chairmen of committees, were occasional scientific papers, and in the evenings, at their conversaziones, what we now call "demonstrations". On these occasions objects of morbid curiosity such as bone tumours, outsize ovarian cysts, monstrosities, and the like constituted the earliest of the items of pathological interest brought before these provincial practitioners.

In the early records of the British Medical Association and in contemporary journals can be found many papers on clinical pathology by William Prout, Golding Bird, Hughes Bennett, and several others including William Addison, then of Malvern, who deserves to be better remembered as a pioneer hæmocytologist. Societies specifically founded for the furtherance of pathology appeared in Reading (1841), in Birmingham (1842), and in London (1846). Morbid anatomy still constituted virtually the whole of pathology, and it was the practical concern of all progressively minded physicians and surgeons as well as the few holders of chairs of pathology. Thus Sir Robert Carswell, the professor of pathology at University College, resigned his appointment in order to become physician to the King of the Belgians.

The natural attachment of pathologists was to the College of Physicians; but, with the emergence of surgery as a scientific subject, morbid anatomy became more and more the concern of the College of Surgeons, the influence of John Hunter in this respect being considerable. In 1799 the Surgeons' Company wisely acquired Hunter's museum; but the important Matthew Baillie collection remained at the Royal College of Physicians until 1935, when it was transferred to Lincoln's Inn Fields only to be destroyed in the late war. Today we have the paradox that at the Royal College of Surgeons the science of pathology is actively pursued but the adherence of pathologists is primarily to the Royal College of Physicians. But the reason that pathologists prefer the qualification of the senior college is that a knowledge of general medicine is of more value to a pathologist than is an acquaintance with anatomy and proficiency in surgical technique.

The seeds of clinical bacteriology and field epidemiology came later and took root in the shelter of municipalities and in the wake of the Public Health Act of 1848, Liverpool in 1898 being the first city to appoint a bacteriologist. There was in fact an early segregation of the bacteriologists, a trend which has recently reappeared with the formation of the Public Health Laboratory Service. An important unifying influence, however, was the foundation of the Pathological Society of Great Britain and Ireland in December, 1906, and the society has done much not only to provide a valuable stimulus to experimental pathology but also to keep the morbid anatomists and the bacteriologists together. The tradition at this time was still very much one of clinico-pathological correlation. "I am old fashioned enough" wrote Rickman Godlee [3] in 1907 "... to think that the chair of pathology should not be divorced from clinical medicine, and I should like to see our professor of pathology provided with beds at the hospital". And then he

* Part of a presidential address, entitled Traditions and Trends, given to the Association of Clinical Pathologists.

1. Alcock, T. *Trans. Ass. Apoth. & Surgeons-Apoth. Engl. & Wales*, 1823, I, xciv.
2. Farr, W. *Brit. med. Almanack*; p. 145. London, 1837.
3. Godlee, R. J. Past, Present, and Future of the School for Advanced Medical Studies of University College. London, 1907.

added "But I should also like to see him so well paid that he is independent of private practice".

Only after the first world war was a serious attempt made in the non-teaching hospitals to provide a pathological service on the lines of those which had in the course of time grown up, although in a non-integrated fashion, in the university hospitals. But whereas the latter pathologists were partly or wholly subsidised by the universities those in the non-teaching hospitals were mostly compelled to seek their own living and even contribute to the upkeep of their laboratories, either as clinicians or in such stable sidelines as throat-swab examinations and water and milk analyses which municipalities were prepared to farm out. Many a physician has been launched on a meteoric career from the ramp of the hospital laboratories. Others, however, retained the double career in medicine and pathology, providing a competent and meritorious laboratory service to their hospitals.

Our Association of Clinical Pathologists—which, curiously enough, like the British Medical Association and the Pathological Society, originated essentially as a provincial society—has endeavoured to serve as a cohesive between workers in all disciplines of hospital pathology, at a time when the profession generally is tending to become more and more fragmented.

The regimentation of the nation necessitated by total war encouraged the idea of rigid organisation in all walks of life, and the medical profession did not escape. The National Health Service Act of 1946, while it has done much to encourage and recognise specialties which previously were underdeveloped or ill defined, has at the same time facilitated the erection of barriers between the specialties. Thus it is now no longer easy for a clinician to acquire some training in pathology without prejudicing his position on the clinical ladder, and the reverse is true for the would-be pathologist. This could be readily remedied by the creation of more hybrid posts.

INFLUENCES ON PATHOLOGY

Since the late war pathologists have exhibited a certain anxiety concerning their future position in the world of medicine, and this has found expression in a demand for the creation of an additional corporation expressly to safeguard their interests. It may be helpful to examine the present position and to ask ourselves what are the influences at work today which are likely in the future to modify the career of the pathologist? This, assuredly, is a most important question, because the only certainty we have is that the practice of medicine will change. What manner of men do we visualise as our successors in say fifty or a hundred years from now? Are they to be scientists or clinicians, or a mixture of the two? Are they to be doctors or technicians, or will they continue to be precariously balanced?

The factors which are likely to modify our careers may be considered briefly under four headings.

The National Health Service Act

No-one would deny the many advantages of the Act of 1946; but the fact remains that we medical practitioners are dependent now for our livelihood on the good will of Parliament with the advice it receives from commissions, the public, and the Press. It is certain that, through shortage of money, pathologists will for many years to come be restricted in space, equipment, and personnel. Our colleagues, the technicians, are paid at rates unfavourable by comparison with those in pharmaceutical houses, in industry, and even in other Governmental departments. We mostly work in antiquated and overcrowded premises and in fact after eleven years still await the first of the post-war hospitals. We are near the end of a long and expensive queue.

The multiplicity of diagnostic tests, the scarcity of qualified technicians, and the general understaffing of the laboratories, all combine to flood the pathologist with routine investigations so that he does not have the time to digest and prepare useful pronouncements upon the material at his disposal. He should be both a trained observer and an investigator, but instead he tends to become just another pair of hands. Yet who better than the pathologist can help bridge the unfortunate gulf which is growing daily between the hospitals and the general practitioners? He is qualified to help in reducing substantially the cost of the drug bills by rendering treatment less empirical.

The Changing Face of Medicine

Advances both in diagnosis and treatment affect our departments from year to year. The greatly increased use of blood has turned laboratories into miniature warehouses for its retail, while the plethora of antibiotics and the errant behaviour of various domestic bacteria have altered the face of clinical bacteriology. The advent of radio-isotopes, the science of immunohæmatology, and the specialised nature of some forms of exfoliative cytology have created new demands on laboratory time, while chromatography and electrophoresis call for extra bench space. Automation has already robbed the technician of some opportunity for the exercise of skill, and it is not impossible that the use of rapid diagnostic procedures will spread in this country, as in America. It is difficult to plan a laboratory for the future, still more so to legislate in our specialty.

The Universities

The role of the universities in pathology, as in all other subjects, has been to foster research, more especially in the experimental field. Pathology, however, is both a preclinical and a clinical subject, spreading over the whole of medicine. The principles of pathology are taught in university departments which are sometimes detached from hospitals: the practice of pathology, which is clinical pathology in the true and wider sense of the word, is taught in the wards, in the laboratories, and in the postmortem room.

The professors of pathology have done their best to cover this wide field, and the siting of the department, its staffing, and their personal inclinations have usually determined the direction in which the department has advanced. Often the holder of the chair finds himself in a quandary, for the university demands of him experimental work but his colleagues ask for help with their patients. In a hospital the patient comes first, in a university research takes priority.

There is a school of thought that holds that chairs of pathology should be reserved for experimentalists and that hospital pathological appointments, whether in histopathology, bacteriology, chemical pathology, or hæmatology, should remain in the Health Service. A schism along these lines might permit of more time for experimental research, but for all other reasons it would be unfortunate. Indeed, many professors who are moved in the direction of experimentation dislike segregation and find that to have some routine and teaching duties

serves to maintain their interest in clinical problems. The universities could of course be asked to provide—as in some places they do—chairs in each discipline and a special chair in experimental pathology. Sometimes routine duties have been deputed to readers and lecturers; but this is an undesirable practice, understandable perhaps in the days when these subspecialties were relatively insignificant sidelines undertaken by part-time men but having no place in a modern hospital centre. In integrating their laboratory services, teaching hospitals often experience difficulties which some have overcome by appointing a director of the clinical laboratories who is responsible for all routine work, the specialised professorial departments being available to deal with the more abstruse problems and the "routine of tomorrow". This obviates the undesirable practices of having fractionated reports on single specimens and of demanding multiple venepunctures when one would do, and at the same time it makes for a more speedy and intelligent handling of the clinical investigation. Segregation of laboratory services, however, is almost the rule in the eastern half of Europe, hæmatology being usually deputed to a clinician with a penchant for the counting-chamber and the Romanovsky stain.

The advocates of separatism argue that these are fundamentally distinct subjects, that no one person can master them all, and that hospital medical staffs should be able to piece together fractionated reports; but they take no account of the fact that this is asking too much of general practitioners who expect and deserve the help of hospital laboratories. A modern hospital unit must provide such an outpatient service, and teaching hospitals have no claim to be exempt from this important duty. Clinical pathology as a concept means the integration of hospital laboratory services by men who, while they may have specialised in one branch, are nevertheless sufficiently cognisant of the others to be able to advise on a report.

Research

There is an impression amongst those in the non-university hospitals that research can have little support unless it is carried out in university departments or with the formal backing of the Medical Research Council. I do not think that hospital pathologists have neglected their opportunities, but more might be achieved if our initiates had more training in the experimental method and if there were better possibilities for coordinating research in our departments. Perhaps it was a mistake not to accept ten years ago the idea of a national service in hospital pathology, for many of us have envied the esprit-de-corps in the Public Health Laboratory Service where the man at the periphery is made to feel that he is an integral part of the whole. While I think our wish to throw in our lot with the clinicians was both right and wise, there is a real need for more coordination of pathological research; and an organisation of pathologists—why not the Association?—could with advantage effect this desirable end.

THE CLINICAL TRADITION

The pathologist stems from a clinical tradition, and only within living memory has he sacrificed the care of patients in order the better to pursue their interests in the laboratories. His overall but indirect clinical responsibility remains high and it would be unfortunate if the service in pathology failed to attract men and women of the requisite calibre. The pathologist who lacks an adequate knowledge of clinical medicine fails in his duty to patients and he is not fully qualified to exercise medical supervisory control of his department. Zeal for technical proficiency so that he may "hold his own" with his symbiot-colleagues, the technicians, should be no excuse for abandoning that postgraduate training in clinical medicine which all consultants need to acquire. The technical work in hæmatology, bacteriology, and chemical pathology is bound in time to be undertaken more and more by technicians, and it is for this reason that some see the eventual extinction of what is now commonly called "clinical pathology".

In the matter of semantics—let me parenthesise—we have three separate usages for the words "clinical pathology" and this has given rise to much confusion. In Osler's sense it means the correlation of pathological findings with the clinical picture; this is now seldom employed. Secondly, it is used as a synonym for "hospital pathology". Thirdly, it is used to describe clinical bacteriology, hæmatology, cytology, parasitology, and sometimes (more particularly in the United States) chemical pathology in contradistinction to histopathology. I am not one who would jettison the term "clinical pathology", because I believe it is expressive of our insistence on the principles of a comprehensive basic training in the several branches of hospital pathology and of the medical supervision of hospital pathological services. Hospital pathology is indivisible, and pathologists who work in hospitals are all, in my view, "clinical pathologists". To create a fundamental cleavage between morbid anatomy and clinical pathology (in the restricted sense of the word) and revert to the Continental system would, I believe, constitute a retrograde step. Nevertheless, this is a trend. A more realistic division is between the experimentalist and the hospital pathologist, but this too is undesirable; in fact nothing would be more unfortunate than that this should develop, for the Health Service pathologist might well degenerate into an automaton.

A SEPARATE COLLEGE?

The widespread desire amongst British pathologists today, especially the younger men, for a college of pathologists is understandable. The underlying motives would appear to be, firstly, the desire to be enfranchised (that is to say, to have a vote in the government of their specialty), and secondly the need of a higher examination. With a State service in medicine, and in a country that is traditionally class-conscious and qualification-ridden, these are not ignoble motives.

So far as enfranchisement is concerned, it is commonly held that it would require a college for pathologists adequately to express their views; but the Association of Clinical Pathologists has for several years spoken on behalf of hospital pathologists both direct to the Ministry of Health and through the Joint Consultants Committee. A request for a place on this committee—which, be it noted, is not a statutory body and has no representation of specialties upon it—is as likely to be granted to the Association as to a college of pathologists; and, if this is desired, now would be the time to press for it. The facts that pathologists constitute the fourth largest specialty, have peculiar administrative responsibilities in the hospital service, and have close relationship with general practitioners and with the public-health service, would justify pressing such a claim.

In this Association we are, I know, all grateful to the president of the Royal College of Physicians for having revived the committee on pathology, the institution of which we owe to Lord Moran, and for having shown his desire to explore all avenues by which the traditional ties of pathologists with his college can in this changing world of medicine be strengthened. Members will have noted that he has recruited his committee in accordance with out solicited recommendations. If a solution can be found within that college to the problem of a "higher" qualification for pathologists, and should there then be no need of a further medical corporation to represent pathologists, it might prove feasible to set up a more formal link between the College and the Association. At the moment the pathologist is not alone in being under-represented in the Royal College of Physicians. Joint committees of the College with elected representatives of these specialist organisations might serve a useful co-ordinating purpose and so prevent further fragmentation of the profession with its attendant dangers.

The problem of qualification is more difficult. The demand from pathologists has been for an examination of the same standing as the M.R.C.P., the pass-rate of which is of the order of 12%. If it is to be similar to the M.R.C.P., then it will have to be designed to be taken early on—in fact designed to pick out the best available candidates for *training* in pathology. I wish to stress this point because, while the M.R.C.P. is with justification called a "higher" examination, in that its purpose is to select high-level candidates, there is a widespread mistaken idea that it is the hallmark of the trained physician. The intention of the membership committee was that the examination should be for the purpose of selecting candidates for training in medical specialties. In recent years some have doubted if hospital pathology is a medical specialty; but, by definition, a physician includes all who practise the healing art, as distinct from surgeons. Perhaps it would be a mistake to plan an examination to test competence as a consultant pathologist, because more than in any other medical specialty the pathologist needs to be unfettered in his curriculum and outlook. Rigid canalisation in training might well prove fatal in a subject which demands original work and requires workers with diverse trainings. The same objection, however, does not present itself if certification is substituted for examination.

When, just over six years ago, we considered the question of an academic body to represent pathologists I said that I believed that the clinical part of the membership examination presented a particular difficulty for pathologists, who are so often by temperament attracted to the bench rather than to the bedside. It is often in fact more than a difficulty, it is a deterrent.

The pathologist who has started on his road might expect to be able to claim a partial—though not a complete—exemption from this part of the ordeal at the price of an additional viva-voce examination designed to search further into his capabilities as a pathologist. As matters are at present, a pathologist who spends too much time in the wards in an endeavour to acquire his M.R.C.P. runs a risk of neglecting his laboratory training, and a candidate equipped with this qualification, when appearing before appointment boards, is under some suspicion of not being a bona-fide pathologist. It seems a pity if the M.R.C.P. examination cannot be modified to suit the special needs of pathologists—not, I would emphasise, with a view to making it easier for them but to ensure that the best potential pathologists are chosen.

The past half century has brought a major change into medicine which is likely to be progressive. No longer are advances exclusively the prerogative of the clinician but they are now shared with the medical scientists of whom pathologists may reckon to be a part. At the moment laboratory workers, who have been deterred from sitting for the membership examination, may expect, if sufficiently eminent, to be admitted into the College on published work; but often this is many years too late. A revised form of membership examination designed to pick out for training not only clinicians but medical scientists would do much to improve the morale and status of the latter and would ensure that they had a share in the College life during their active years; but if it is felt that the Royal College of Physicians should now be restricted to serve only the interests of those concerned in the medical care of the patient—that is to say, physicians in the present-day meaning of the word—then there is no alternative but to initiate an academic body for pathologists, and it should be done without further delay. It would indeed be unfortunate if undue emphasis on the clinical examination were to be the reason for discouraging medical scientists from adhering to this college, especially when one recalls that clinical examination is a development of only the past 140 years and that revolutionary methods likely to alter the technique of the clinician may be just round the corner. The clinician and the scientist, having parted company in recent years, may through force of circumstance yet again converge.

In this country we have evolved an attitude towards hospital pathology in which we believe that a pathologist, whatever his subspecialty, should receive some training in all branches, and this is more than ever necessary since the inception of the National Health Service Act. We should give substance to our belief and, with the help and benison of others, should cause to be instituted an examination designed to test a candidate's ability for a career in pathology. Pathologists should determine the nature of this examination, and they must be in a position to modify the training in the future. If the Royal College of Physicians is unable to provide this examination—and this appears to be the fundamental issue—then an appropriate organisation must be set up. The precise nature of this body would have to be considered carefully and not by us alone. We would have to consider the long-term as well as the short-term effects not only on our specialty but on the profession as a whole.

In the course of time, the pathologist has evolved into the consultant's consultant, and therefore we should seek a formula which permits of his influence being diffused throughout all branches of the profession. I am sure such a solution can be found and that it will be worthy of our times, which demand a considerably closer integration in medicine than we have hitherto enjoyed.

". . . Few working premises stand idle for longer in the year than university buildings, few workers are longer away from their jobs than university students. In former days, in theory at least, students read in the vacations; now they take paid employment. Should they have to, or should university study be regarded as a full-time paid employment in itself? If the investment it represents be taken seriously, one is driven to the conclusion that it should."—Prof. H. G. DENT, *Observer*, Oct. 12.

MOTHERS WITH CHILDREN IN A PSYCHIATRIC HOSPITAL*

T. F. MAIN
M.D. Durh., D.P.M.
MEDICAL DIRECTOR, THE CASSEL HOSPITAL, HAM COMMON, SURREY

Now that most pædiatric hospitals and wards encourage mothers to visit their children, or even admit the mother with the child, it seems odd that so much less attention is paid to the disruption in this same mother-child relationship when it is the mother who has to go to hospital.

In this country—though not in some others—a mother admitted to hospital is usually cut off from contact with her children, whether she wants it or not. In some hospitals it is not thought proper for children, and especially young children, to go to see their sick mothers even on visitors' day. The reasons vary: a sick woman should not be bothered by children; children increase the risk of infection in a hospital; they are too noisy and disturb other patients. Such reasons are based on the partial truth that children are a nuisance; but others are based on a different half-truth—that the children will be harmed. People say that a hospital for sick adults is no place for a healthy child; that a visit or a stay there will prove disturbing to it; that it cannot get from a sick mother the attention it should have; and that it would be better with its granny.

No-one would deny that for many situations these two arguments are valid; but when applied to *all* hospitals they recall the hostile ratiocinations common a few years ago when it began to be generally mooted that the child in hospital should have frequent visits from its mother. These, too, were always logical, but they underestimated the importance of the child's relationship with its mother to its mental and physical health.

As a student I had been impressed by James Spence's insistence on the twin dangers of separating mother and child; first, and more obvious to the child's physical and emotional health, and second, but as fateful, to the mother's confidence in her future capacities as a mother. In 1948, therefore, when a woman patient at the Cassel Hospital asked if she could bring her toddler son who had none other to care for him, perhaps it was his teaching, as well as my interest in the work of René Spitz in New York and Anna Freud and John Bowlby in London that made me agree. Beginning as an unusual occasional occurrence, the admission of a mother with her infants or young children has since come to be a common and unremarkable element of the life of this psychiatric hospital for adults.

A STUDY OF MOTHERING

We started admitting children at a time when we were experimenting with the hospital community, to see whether it could become less of a social vacuum—more a place of treatment and less of a retreat from the stresses and strains of domestic and industrial life to which a patient must inevitably return. Just as it seemed important to keep a man patient in touch with his job and to treat him for the difficulties he might meet there, so it seemed important that a mother should be kept in touch with her job, and the children who were part of it.

Soon we learned that admitting infants and toddlers with mothers had two effects which arise out of the ordinary ambivalence towards children: not only did it help to maintain and promote the positive elements in the mother-child relationship, but also it prevented escape from, and concealment of, the negative elements. By 1955 it had become clear to us that to admit the mother by herself was sometimes to collude with her hostility towards her children and with her wish to be separated from them. Bringing the children into hospital presented the mother's problems with her child in daily living form and often as a matter for urgent treatment. The mothers were now bringing their anxieties to us, and we were no longer helping them to hide in hospital from them. This was, of course, more painful for all, but it allowed treatment to be more effective, for we no longer conducted it in a vacuum. Gaining in confidence, from 1955 onwards we made it a condition of admission that mothers should bring their babies and young children with them; and few exceptions have been necessary.

At first we were not aware that we had given ourselves an unusual opportunity for studying disturbances of mothering. Up to 1954 we were not even aware that we were studying disturbances in mothers, but rather saw ourselves as treating women patients whose children's admission was simply an unusual additional feature of their stay, and whose illnesses were of a general neurotic order and not particularly centred in the mother-child relationship.

Up to 1955 we had no special experience of puerperal breakdown, where the impact of the child and the assumption of mother roles are in the forefront of the illness, but now we began to accept requests for treatment of puerperal cases—puerperal depression with apathy towards the baby but maintained interest in an older child, in puerperal anxiety states with hatred of the baby and infanticidal wishes, and so on. We have not, however, admitted cases of gross confusional insanity or schizophrenia of certifiable extent.

So far as we knew, there were few precedents for admitting women with puerperal states together with their infants, and I must acknowledge the help of a consultation with Dr. Gwenyth Douglas who, in a maternity ward of the West Middlesex Hospital, had worked with parturient mothers who had difficulty in accepting their babies unless they were cared for in part by nurses.[1] To begin with, we cautiously admitted one or two puerperal mothers and their babies and then, finding our feet, began to welcome more and to treat them by individual psychotherapy. The mothers are usually offered individual psychotherapy informed by psychoanalysis, but last year some mothers were admitted together for group treatment, all bringing their preschool children.

PRACTICAL ARRANGEMENTS

In this 100-bed hospital we have at the moment 18 toddlers or infants. The hospital is thus not mainly concerned with mothers and children, and there is no special unit for them. They live as ordinary a life as possible, cheek by jowl with other patients; but the hospital building seems particularly well suited to this arrangement.

Apart from the central administrative services, common-rooms, diningroom, workshops and entertainment rooms, we have some 20 single rooms and other rooms with 2, 3, 4, 5, and 6 beds; and the whole hospital is easily arranged into four units of approximately equal size, with some 25 beds in each. Each of these four units (or medical firms) has its own medical and nursing staff and patients. Each firm, under a

* From a paper read before the psychotherapy and social psychiatry section of the Royal Medico-Psychological Association on March 27, 1958.

1. Douglas, G. *Lancet*, 1956, i, 124.

consultant, is entirely responsible for its own area and its own affairs, for its own domestic and nursing arrangements, and its own methods of treatment.

The maintenance, repairs, and redecoration, the daily cleaning and arranging of the firm area, is the responsibility of the firm; and the daily work cannot be carried on without the help of the patients, who are largely responsible to themselves and to each other for deciding what is needed, what gets done domestically, and who does it. Each firm has a small annual budget which it is free to spend on internal decoration, curtain material, drying arrangements for nappies, and so forth.

The patients in a firm meet together with a sister weekly to discuss what shall be done, and by whom.

In this setting the problems created by mothers and children, and their special needs, are discussed weekly by them and others, and appropriate arrangements are made. Both patients and staff are aware that the resources of each firm in money, accommodation, and labour are limited, and that the solution of such everyday matters as the need for quiet when a baby is sleeping, for a laundry and ironing service, or for the repair of furniture is a matter for decision by and cooperation from all. Anxious mothers can here get the support of others, and when a mother is felt to be neglecting her baby both nurses and patients can plan to help. Patients are exposed to the criticism of others and can appeal for support from each other. The friendships between patients and the ventures on which they embark together do much to compensate them for the corporate discipline that they demand of each other, rather as in a family.

The hospital has also a patients' central organisation, and each firm is responsible for some general service for the whole hospital, such as food preparation, or washing up, cleaning and maintaining common-rooms and other areas. The patients' central organisation has arranged that mothers and children should have special mealtimes, so that the nuisance of noise, jammy fingers, and spilt milk is shared only by mothers and not by other patients, that toys and disorder should be confined to *one* of the common-rooms, that guards and railings are erected as necessary, that extra milk for children should be available, that the children's television hour should be sacred for them, and so on.

Each mother and child live together in their own room arranged (in James Spence's words) " to give an atmosphere of domestic comfort " and even homely disorder " which would not be alien to it ", to which the mother brings the child's own cot and toys from her home. With or without help from others she cares for it, washes for it, prepares its food in the ward kitchen and nurses it. If she wants to go out in the evening or to her session with her psychotherapist, a baby-watcher will be needed, and of course among the younger women in the hospital a willing unqualified but eager apprentice may be found. Every morning sees mothers pushing out their children in prams, and washing and hanging out laundry in the hospital grounds. Mealtimes see mothers feeding babies on their knees or in their own high chairs with hospital adult food or milk meals they have prepared themselves. Afternoons may see the mother soothing her child to sleep in a darkened room, playing with it in the garden, or taking it to a staff play-session. Evenings may see the fathers of these children as visitors eating at the hospital with their wives, handling and potting the babies or taking their wives to a cinema. Weekends may see the husband staying the night with his wife as a lodger in the hospital, or the mother with child spending nights at home, cooking the Sunday dinner and seeing the older children.

It is remarkable how many mothers who, in a more orthodox hospital context, would be very ill, passive, and dependent, are able to carry on fairly actively supported by each other and by their psychotherapy. The hospital tries at all times to possess neither mother nor child, but to offer independence and to provide support only where and when it is necessary, and to be the agent of the home and family rather than to replace these as the centre of the patient's life.

We have admitted up to three children with one mother and occasionally we have had to arrange classes for older children, but it is more usual for the mother to have only one young toddler or infant.

A single room with space for a cot is suitable, or a double room where there is more than one child. Rarely, where the father too has been psychologically ill, we have admitted whole families and have used two rooms. Where a mother and a child have to share a room with another patient, a childless patient seems to share more successfully than another mother-child pair, and this seems to be no greater hardship for the childless patient than any other sharing of a room. Occasionally we have housed a child in a different room from its mother, but this is rare. Our doubts about the wisdom of having toddlers sleep in the same rooms as their mothers are the less because such arrangements are almost the rule in our patients' own homes.

Mothers and children are admitted in the ordinary way on request from their family doctors, child-guidance clinics, psychiatric outpatient departments, mother and child-welfare clinics. We have found that a home visit by the senior nursing sister who is later to care for the pair in hospital and full consideration of her findings at the case conference help to anticipate the nursing problems and to decide whether the mother should be admitted with more than one child, and how far the husband also should be brought into the treatment situation. It helps to introduce the hospital as an adjunct rather than an alternative to the home, and to allow the husband to share from the first in the admission procedure. The sister's visit allows her to tell the family what they should bring in the way of high chair, cot, pram, toys, and so forth, and makes plain from the first by suggesting frequent visiting of wife by family and family by wife that admission to hospital does not imply the possession of any family member by strangers, but rather the offer of treatment within continued family relationships.

Ten beds have been allotted by the regional hospital board for children whose behaviour disturbance is such that they can truly be regarded as in need of treatment. Other children, less disturbed, are admitted as lodgers. The mothers of children under four bring cots and other equipment and do their own baby laundering, so that the average cost of maintaining these children in hospital is £2 5*s*. per week. For older children who occupy hospital beds the average cost is £8 10*s*. per week. These simple averages conceal the fact that substantial economies in nursing care have been made possible by allowing patients in hospital to take active roles, one of which is mothering.

With children's upsets and infectious diseases none of the psychiatric staff have felt confident, and the hospital has gladly enlisted the help of Dr. C. A. Baggley, a general practitioner on whose panel the children are registered, and the maternity and child-welfare clinic at Ham. We have drawn freely on the advice of Dr. Eric Pereira, the medical officer of health for Richmond, in dealing with outbreaks of infectious diseases.

The average stay of a mother and child in the hospital is 6·05 months (S.D. 1·81). Some of the children are known to have been under emotional stress because of disturbances in their mothers, and all but a few have benefited indirectly but quickly from improvements in their mothers' attitudes. They flourish in hospital, and for them and their mothers the stresses both of lengthy separation and of reunion have been avoided. It has been possible to avert the explosive family-catastrophe common after puerperal breakdown whereby father, mother and baby are flung apart and scattered among relatives, neighbours, hospital, foster parents, or local authority homes.

The general benefits to mother and child are clear, but it may well be that this method of handling psychiatric disturbances in mothers contains subtle snags. Follow-up by letter indicates that the mother/child relationship is

not disturbed when the pair return home, and that the children settle down quickly and unremarkably alongside their mothers in their homes. There are indications, however, that older children may miss the hospital for some days after their return. It has been well said that for a baby home is simply where the mother is, but follow-up visits might reveal subtle problems of resettlement of which we are as yet unaware.

THE OTHER PATIENTS

In the early days both mothers and children met with complex emotional receptions from the other more or less seriously disturbed adult patients, whose own miseries and regressed needs led to an ambivalent warmth about these sick mothers and children. Some patients felt deposed and displaced, with the babies as their rivals for the attention of the staff; others objected that the hospital was bad for children anyhow because of the neurotic behaviour of the rest of the community; others said their cure was jeopardised because it depended on the peace and quiet now endangered—especially at night—by the new arrivals. Others, again, spoke on behalf of the mothers, whose illness, they claimed, was due to the demands made on them by their offspring. The patients' attitudes, expressed in the minutes of their firm meetings and of their central committee, veered between the one extreme that children were dangerous intruders who should be kept in special departments, well disciplined, and not allowed to mix with adults, and the other extreme that their noise and disorder should at all times be tolerated.

With the working through of these attitudes, by the summer of 1955, sensible arrangements were made of a fairly ordinary domestic kind. Men patients had erected swings for the children, made a table for the nappie boiler, and helped arrange drying-racks, clothes-horses, clothes-lines, and blackboards. But when cold weather drove the children indoors from the grounds emotional extremes could again be noticed. The patients' executive committee again considered compulsory quiet periods, a special unit for mothers and children, a noise room with a rota of mothers to supervise it, and excluding children from the television rooms—as well as, on the other hand, creating special programmes and privileges for them which ignored the rights of adults. Ultimately, few of these recommendations have survived.

With the passage of time, mothers and children have ceased to become special, and strong emotional attitudes towards them, either tough or sentimental, have vanished. Washing, drying, and eating arrangements, one common-room for children's toys and apparatus, a play period supervised by a psychologist, and arrangements for mothers to keep in touch with their own homes have become routine. Issues that a year ago were hot have now cooled.

But though, for patients and staff alike, settlement of the affairs of mothers and children has become part of the daily work of the hospital, this work is not, and cannot be, effortless. Often in the past, and still today, staff and patients have been confronted with problems of feeling and behaviour, underlying relatively trivial practical issues, whose solution has not been easy.

We have not found our other patients disturbing to the children. The neurotic patient's difficulties lie mostly in relationships to other adults and rarely preclude the ordinary ambivalent altruistic responses that young children evoke in most people. They have no close or intense contact with the children unless they wish it, for children belong to their mothers and live and play in their vicinity. I know of only one adult patient who was refused admission out of consideration for mothers and children—a man with homicidal impulses towards children; and I am not sure that even here this decision was necessary or wise.

THE FUTURE

Because we do not admit chronic cases or those under certificate, we have no experience with grossly psychotic mothers and their children. Nor are we sure that our procedure could suitably be used for all disturbed mothers. Some of our patients needed psychotherapy before their anxieties were lowered sufficiently for them to agree that their children should accompany them; and sooner or later we shall meet cases (say, autistic mothers) in which the child would be better separated from the mother than made to coexist with her. But what has been impressive is how much can be achieved with these women. Some of our mothers had been certified in the recent past and many had been in mental hospitals. Many had found mothering an impossible task and either they or their husbands had sought foster-parents for their infants. In the hospital, severely disturbed, terrified, depressed, or impulse-ridden women become able to mother their children with increasing mutual benefit, and eventually to help other mothers and children.

I would add that psychiatry needs opportunities to study severe disturbances of the mother-child relationship. Much has been written about the psychology of women, and also of infants, but remarkably little on mothering and its disturbances; and most of what has been written is concerned with the baby's needs rather than the mother's. Perhaps this is partly because it is our usual practice to separate mother and child when there is an acute disturbance of mothering. Admitting mothers and children to psychiatric hospitals may therefore be an important development for the study of these disorders.

Public Health

The Second Quarter

REPORTS on the second quarter of this year in England and Wales,[1] Scotland,[2] and Eire [3] include the following figures (the figures for the corresponding quarter in 1957 are included for comparison):

—	England and Wales		Scotland		Eire	
	1958	1957	1958	1957	1958	1957
Birth-rate (per 1000 population)	16·9	16·6	19·9	19·5	22·6	22·8
Death-rate (per 1000 population)	11·1	10·6	11·8	11·2	12·6	11·4
Infant-mortality rate (per 1000 live births)	21·3	22·3	27	27	36	32
Tuberculosis death-rate (per 100,000 population)	9·4	9·5	10	12	24	26

In England and Wales in 1957, provisional figures show a record low number of 6 deaths from diphtheria. There were 227 deaths from acute poliomyelitis, 125 of which were in persons between 25 and 45. Accidental deaths registered in the June quarter numbered 3819, an increase of 566 over the figure for the June quarter of 1957.

1. Registrar General's quarterly return for England and Wales, no. 438. H.M. Stationery Office. Pp. 28. 2*s*.
2. Quarterly return of the Registrar General, Scotland, no. 414. H.M. Stationery Office. Pp. 32. 2*s*. 6*d*.
3. Quarterly report on Births, Deaths, and Marriages, no. 378. Obtainable from Government Publications Sale Office, G.P.O. Arcade, Dublin. Pp. 32. 6*d*.

In England Now

A Running Commentary by Peripatetic Correspondents

"WHEN that I was and a little tiny boy" (way back in the 'nineties), my mother used to read to me from a book called *What Makes Me Grow*. As far as I remember *Go* would have been a more accurate title, for the mysteries of growth were not probed deeply, but I got as clear a notion of the pulmonary and systemic circulations and the four-chambered heart as I did, about the same time, of the high and low pressure cylinders on the steam-roller on which I once proudly rode. And when I came to man's estate (with a hey! and a ho! and all that) my young sucked in their physiology from the admirable *How You Work* and their embryology from *How You Began*. I think they were well served; but now I'm in the sere, the yellow (and the glass goes down for ever) how fares it with the neo-Elizabethan, avid as ever for material self-knowledge? I don't really know, but I have an idea that for the true child of our time hearts, lungs, livers, kidneys, and even central nervous systems are tedious stuff, fit only for decaying elders. Glands and the pelvis contain all the anatomy and physiology worth his attention and a shoal of writers, illustrators, and diagrammatists see that he (and she) gets it. All may be for the best. Time may—but probably won't—show. We all have to be ready to discuss with sophisticated seven-year-olds, in good, solid, down-to-earth Latin, the site, shape, and functions of the uterus (pronounced yew terrace) or the sea minnle v sickles. The odd thing is that when the womb turns up in the *Te Deum* or the sturdier names for the male organ in Shakespeare, they may well be more mystified than were the unenlightened young of the notoriously prudish generations now, luckily, passing away.

* * *

My friend Michael has just returned from a holiday in Italy, where medical care seems to be more flexible than under the N.H.S. He was living in a small village hotel when he became ill and in the morning asked the cameriera (chambermaid) for advice.

She immediately took command and informed him that he had a fever which would be cured by a "puntura di penicillana". The assistant cook was then dispatched to town (riding on the pillion of her fiancé's 'Lambretta') and they returned with a supply of the wonder drug which was then injected into the patient's buttocks by the chambermaid in person. The whole operation was eagerly watched by the cook and her boyfriend. The package containing the penicillin clearly stated that it should only be used under strict medical supervision. After two days there was no clinical improvement and the chambermaid decided on a second opinion; so a physician from the town was called. He duly arrived and seemed entirely unperturbed by the initial management of the case. After solemn deliberation he advised a change to chloramphenicol, which, happily, was effective.

Michael was greatly impressed by the medical care he had been offered, and we both agreed that in this country the most expensively trained chambermaid (even an old Claridge's girl, so to speak) would hesitate to diagnose a P.U.O., then prescribe and administer treatment by intramuscular injection.

* * *

Surprises—pleasant and unpleasant—await the elderly non-clinical medical type who finds himself with mild diabetes. Instead of having to light a young fire and, after cracking a test-tube or two, bespattering the wallpaper or getting an eyeful of hot urine, a little gadget resembling a paper match tells him what he wants to know with no trouble or fuss. On the debit side is what he has to use for bread. It tastes like tired, old nylon stockings which have been boiled for a long time, mumbled between the toothless jaws of aged Japanese crones, then baked in a very hot oven and marketed as a side-line called "meringue-substitute" by a North American multi-millionaire cereal manufacturer: it tastes, in fact, very much like British standard white bread. On the other hand, marmalade is just like marmalade and, although ordinary diabetic chocolate is relatively nauseous, surprisingly, the milk chocolate is indistinguishable (except in price) from real milk chocolate. But whatever sweetening agent is used, there is that lingering, cloying after-taste.

The real solution, I believe, is to cultivate an expertise in the many things he is permitted to take and to keep away from substitutes—to become in fact a gourmet instead of a gourmand. A drawback is that an attempt to become an expert in, say, oysters or French beans, or the 157 types of cream cheese, will probably send his wife round the bend, if she is not there already from having to provide a special diet for him in this standardised world.

* * *

I have been looking for a cottage about eight miles from the hospital. Already I am used to bedrooms on landings, lavatories 100 yards from the house (and through a thicket of bramble and nettles at that), and spiders the size of middle-aged crabs. The only thing I have insisted on is a bath and adequate means of heating water. Last weekend I set off with another address. The sun shone and I was full of hope.

The cottage was timbered and very lovely. I asked about the bath immediately, and without hesitation the landlady took me to the kitchen where a minute little-more-than-a-basin bath stood proudly. She saw my look of amazement and said reassuringly, "My last tenant was 6 ft. 4 in." My imagination folded a long, thin, anguished man into the bath. I made him hypotonic, wrapped his legs round his neck, gave him rubber bones, but completely failed to pack him in. I looked again and said, "No taps." She smiled triumphantly and pointed to a small mobile tank with a heater element. The tank was filled; the flex carried down a long corridor into the sitting-room where it was plugged in. When boiling, the water was run into the bath, where it settled into a half-inch-deep pool. The tank was filled again and the water heated, but by this time the water in the bath was already tepid. And so one went on.

My thoughts twisted themselves into a psychiatric nightmare. I imagined filling tanks and baths, switching plugs on and off, running down corridors, and being cocooned in flex. I leaped into the ice-cold water only to find my backside firmly wedged inside. A shiver ran through me as I imagined the ward round the following day—the bath still attached to me like a snail shell.

I drove at fever heat back to hospital—to the resident's cosy modern flat and a hot civilised bath.

* * *

The discovery of material, probably virus in nature, which, when injected into females of a species of fly, causes them to procreate only females is startling. Apparently the virus selectively kills the male germinal elements. How useful an alternative this could have been to the mass killing of male offspring of the Children of Israel in Egypt. Indeed, instead of the highly scientific appelation of sex ratio virus, why not call it simply the pharaoh virus?

* * *

The trouble about Stock and Gesell is that their approach to child development is too qualitative. The publication of Parkinson's Law has stimulated me to try to express some of the more important concepts in quantitative terms.

The amount of noise (decibels) made by a child is inversely proportional to the strength of the stimulus applied.

The amount of force (ergs) required to remove a child from the room is directly proportional to the degree of secrecy of the topic under discussion.

The probability of inducing car-sickness is a direct function of the length of the journey and of the third power of the amount of attention directed to the subject.

The force of a temper-tantrum is the product of the bloody-mindedness of the child and the like-mindedness of its parents.

The half-life of a birthday present is inversely related to its cost.

Letters to the Editor

SHORTAGE OF JUNIOR HOSPITAL STAFF

SIR,—The letter from Dr. Savidge and his colleagues (Oct. 4) is an indication of the increasing difficulty peripheral hospitals are having in finding junior medical staff. That the situation is serious was illustrated by a news paragraph in *The Lancet* of Aug. 16 which stated that a group of hospitals in York had been compelled to restrict their admissions to emergency and urgent cases because of the lack of house-officers.

Dr. Savidge and his colleagues have dealt with one aspect of the problem; another is to be found in the increasing number of newly qualified graduates who go abroad to do their preregistration jobs; surely it would be possible to discourage this habit and without encroaching too much on individual liberty. In these days when grants play so large a part in student finances it would not seem too much to expect that the newly qualified should complete their preregistration years at home. Work overseas attracts not only the youngest members of the profession, or some of them, but, to judge from recent correspondence in the *Sunday Times*, appeals also, though less directly, to some of our older colleagues who would encourage a scheme to second registrars or senior registrars temporarily to posts abroad, thereby enhancing the prestige and influence of British medicine and helping, incidentally, to solve (or shelve?) the registrar problem.

Sympathetic as one may be to such a scheme, especially in relation to time-expired registrars, it seems necessary to suggest that it should be invoked only after all our hospitals at home have been adequately staffed. Time and again registrar posts at peripheral hospitals are advertised without any applicant coming forward; while this might result from an absolute lack of registrars, or would-be registrars, it seems more likely that the lack is relative and that applicants, on a sellers' market, can afford to ignore (or, as they believe, in their own interests, must ignore) any non-academic, non-teaching-hospital job. If this latter view is correct there is much to be said for the suggestion that a necessary condition for promotion from registrar to senior registrar, and senior registrar to consultant, should be a period of duty in a peripheral hospital in each grade. It is pathetic that so many registrars know that at the periphery they would gain rapidly in experience and responsibility yet feel that they dare not risk departing from the centre and so become forgotten and out of favour.

One must hope that the Working Party on Hospital Staffing may find some answers—not too long delayed—to all our woes, though in its membership the preponderating influence of the academic centre is, once more, very obvious. Some of us who work at the periphery have an occasional suspicion that in Officialdom's view our territory is more remote than any foreign field and that for all the influence we have in shaping policy it might well be so.

Falkirk and District Royal Infirmary. RONALD G. HENDERSON.

SIR,—I read with interest the letter from Dr. Savidge and his colleagues concerning the shortage of housemen at peripheral hospitals. The system of appointment of housemen for the specialties as preregistration jobs in the teaching hospitals is blamed and the solution suggested is to allow doctors from abroad to fill such posts. Surely the answer is a little nearer home: we must recognise the laws of supply, demand, and remuneration which apply elsewhere, and make these jobs sufficiently attractive to draw newly qualified doctors away from the glamour of the teaching hospital. Imagine the response to this advertisement:

"House-surgeon wanted. Salary £800 p.a. [we take a few hundred from the consultant's pay; it would only go in tax anyway]. One or two evenings off guaranteed. Married accommodation secured."

This may seem a little pipe-dream but it is surely a better solution than to inflate the number of junior doctors in this country without in any way trying to reform the status and conditions of work of the newly qualified, which is the basis of the problem.

Westminster Medical School, London, S.W.1. P. J. N. HOWORTH.

TONSILLECTOMY AND POLIOMYELITIS VACCINE

SIR,—In his letter of Oct. 4 Dr. Christie has drawn attention to a most important point. Having seen fatal bulbar poliomyelitis following upon dental extraction in a young child, I think that Dr. Christie's advice might apply to this operation also, so that no dental extraction would take place in a child who has not received at least two injections of poliomyelitis vaccine, unless the condition was very urgent.

Newport Infectious Diseases Hospital, Newport, Isle of Wight. JOHN MILLS.

BANTING UP TO DATE

SIR,—I read your leader on obesity last week with particular interest since the title you gave it is the subtitle of my book, *Eat Fat and Grow Slim*. High-fat diets are on the map again, but few doctors are very happy about them. You have given your readers a fascinating round-up of the subject and particularly the conflicting experimental findings of different research-workers.

Unfortunately the contradictory nature of these findings, particularly in relation to body-water, fat metabolism, and atheroma, has made the problem seem more difficult than it really is, by keeping our attention too close to the laboratory bench.

In other branches of medicine—cancer, for example—we are seeing how the social-medicine people, the epidemiologists, and the anthropologists are bringing out new facts which have immediate clinical application.

A great deal can be learned about obesity from this wider point of view, and too little notice has been taken of anthropologists like Stefansson [1] and clinicians like Pennington [2] and Thorpe,[3] who have shown that high-fat, high-protein, low-carbohydrate unrestricted-calorie diets are the only satisfactory answer to obesity from the patient's point of view, because they are the only diets that can be kept to without feeling hungry.

Stefansson, the greatest living authority on the Eskimo, has lived and worked on such a diet for years at a time. In 1928 he and Dr. Karsten Andersen followed an all-meat diet for a year under medical supervision from Bellevue Hospital, New York. They lost their excess weight and their blood-cholesterol fell. Both felt well all the time.

Stefansson has told me recently that since October, 1955, he has been on the B and B diet (Bourbon and Beef) with which he takes—I quote him—"Heavy cream and any size of egg from caviar to ostrich. For our egg helpings the formula might serve: please pass the cholesterol."

Pennington slimmed the overweight executives at E.I. du Pont de Nemours, painlessly and without starvation, on fat and protein but no carbohydrate, in 1950.

1. Stefansson, V. The Fat of the Land. New York, 1958.
2. Pennington, A. W. *Amer. J. digest. Dis.* 1954, **21**, 65.
3. Thorpe, G. L. *J. Amer. med. Ass.* 1957, **165**, 1361.

Thorpe, who was chairman of the Section of General Practice of the American Medical Association last year, read a paper on obesity at the 100th annual meeting of the A.M.A. "The simplest to prepare and most easily obtainable high-protein, high-fat, low-carbohydrate diet" he said "and one that will produce the most rapid loss of weight without hunger, weakness, lethargy, or constipation, is made up of meat, fat, and water. The total quantity eaten need not be noted."

This evidence and the evidence of history is very convincing, but what is needed to clinch the matter now is a long-term prospective study of obese people treated on these lines. This is a subject which might well engage the attention of the College of General Practitioners.

Richmond, Surrey. RICHARD MACKARNESS.

IRON DEFICIENCY IN MAN

SIR,—Your leading article [1] on this subject was extremely interesting and instructive. It is certain that a large group of patients in need of intensive iron therapy are intolerant to the usual available preparations. In fact, the changes of the gastrointestinal mucosa in iron-deficiency anæmia make it less tolerant than during a repleted state. The new oral chelated-iron compounds represent a distinct advance in the treatment of this very common condition.

I was somewhat disappointed that no mention was made of the most widely explored iron chelate/ferroglycine sulphate complex. Our own clinical experience was indicated in a recent publication: "The therapeutic and performance indexes of ferroglycine sulphate complex ('Ferronord') are optimal in the treatment of iron-deficiency anæmia."[2] It was quite evident that this new oral iron chelate provided the best therapeutic results with the least evidence of side-effects. This was expressed as a therapeutic index which is a useful measurement of the value of any drug.

Our results have been reproduced by a large group of investigators. A long bibliography [3-9] attests to the unanimity concerning the therapeutic index of the oral iron chelate/ferroglycine sulphate complex.

New York. JULIUS POMERANZE.

COMBINED GASTRIC AND DUODENAL ULCER

SIR,—I am happy to read Dr. Billington's analysis (Oct. 4) confirming the fact I recorded in your pages last year [10]—that combined-ulcer patients genetically resemble subjects with duodenal ulcers alone rather than those with gastric ulcers alone.

In earlier papers [11 12] I showed why this should be so, for an analysis of 135 combined-ulcer cases demonstrated that the duodenal ulcer was probably always there first, the gastric ulcer appearing later, usually as a complication of duodenal or pyloric stenosis with gastric retention. Combined-ulcer patients were also shown to have gastric secretion patterns similar to those of duodenal-ulcer patients, and, of course, different from those of the gastric-ulcer subjects. Gastric ulcers complicating duodenal ones appear to be a special variety which should probably be dealt with separately from other gastric ulcers in statistical analysis.

My figures have differed from those of Dr. Billington, however, in that they have suggested that prepyloric ulcers, which I have regarded as a third type of gastric ulcer, have more in common with duodenal ulcers than with "ordinary" or type-I gastric ulcers.

Incidentally, the three kinds of gastric ulcer have quite different prognoses and call for different methods of treatment. Combined ulcers have a particularly bad record of intractability and hæmorrhage.

Royal Free Hospital, London, W.C.1. H. DAINTREE JOHNSON.

THE FRONTIERS OF MEDICINE

SIR,—Professor Stuart-Harris (Aug. 30) said that when he was a student (1930) "it was common to feel that patients were admitted to the medical wards to lie and rot", and Dr. Marshall (Sept. 20) has "very deeply resented" this statement. As one who felt with the Professor and who felt further that many patients were admitted solely for teaching purposes and the exercise of the higher diagnostic skills, may I quote a few figures in support of this view.

Here is an analysis, which I made when a student, of the treatment and outcome of 30 consecutive admissions to two medical wards of a general hospital in 1932.

Treatment received was:

Special treatment (available only in hospital)	6
Routine treatment (available from any general practitioner)	16
No treatment (except rest in bed)	8

Condition on discharge was:

Completely recovered { as a result of treatment	1
Completely recovered { with no treatment	4
Improved { as a result of treatment	4
Improved { with no treatment	2
Unchanged	12
Worse	2
Died	5

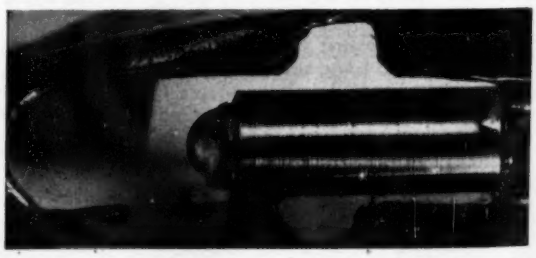
Only 2 cases showed any improvement as a result of the "special" treatment available only in hospital. This is a very small series, but I think it is a fair random sample of conditions prevailing at that time. As regards impact on the student mind, some of us were diverted to the less lucrative but, as we felt, more honest pursuit of fundamental research.

M.R.C. Radiobiological Unit, Harwell. O. A. TROWELL.

FLICKERING LARYNGOSCOPES

SIR,—There is nothing more irritating to an anæsthetist than for the light of his laryngoscope to flicker, and sometimes fail altogether, just as the glottis has been visualised.

This is a rather common failing of the standard Macintosh laryngoscope, and is almost invariably due, in my opinion, to



the fact that it is impossible to get any instrument on to the bulb to tighten it properly.

The accompanying photograph, which is considerably enlarged, shows a small adaptation to the Macintosh laryngoscope blade which has proved to be very satisfactory, and which consists only of filing a small hole into both sides of the blade so that the body of the bulb can be held by a pair of artery forceps, which enables a really tight fit to be made between the bulb and the bulb-holder.

Pietermaritzburg, Natal. J. D. M. BARTON.

1. *Lancet*, 1958, i, 1162.
2. Pomeranze, J., Gadek, R. J. *New Engl. J. Med.* 1957, **257**, 73.
3. Rummel, W., Candon, B. H. *Int. Rec. Med.* 1956, **12**, 783.
4. Feldman, H. S., Rummel, W. *Med. Times*, 1956, **84**, 1329.
5. Dwyer, T. A. *Clin. Med.* 1957, **4**, 457.
6. Clancy, J. B., Aldrich, R. H., Rummel, W., Candon, B. H. *Amer. Pract. Digest Treat.* 1957, **8**, 1948.
7. O'Brien, T. E., Onorato, R. R., Dwyer, T. A., Candon, B. H. *West. J. Surg.* 1957, **65**, 29.
8. Wagner, H. *Landarzt*, 1955, **31**, 496.
9. Jorgensen, G. *Ärztl. Wschr.* 1955, **10**, 92.
10. Johnson, H. D. *Lancet*, 1957, ii, 518.
11. Johnson, H. D. *ibid.* 1955, i, 266.
12. Johnson, H. D. *Surg. Gynec. Obstet.* 1956, **102**, 287.

SALIVARY PRECIPITATING ANTIBODIES IN SJÖGREN'S SYNDROME

SIR,—I was interested to read Mr. Jones' article of Oct. 11. I think that certain observations of mine throw light on the relation of these phenomena to rheumatoid disease.

There is a lot of evidence that Sjögren's syndrome is a manifestation of systemic lupus erythematosus. For example, they are conditions that occur predominantly in women; rheumatoid arthritis, arthralgia, peripheral vascular symptoms, and purpura commonly occur in both. Furthermore, in both conditions raised gamma-globulin levels, giving positive precipitation and flocculation liver-function tests, are found. Also leucopenia and thrombocytopenia occur in many cases of Sjögren's syndrome, and out of 28 cases seen at the Bristol Eye Hospital L.E. cells in the peripheral blood were found in 10; no doubt L.E. cells would be detected in more of these patients if looked for at intervals for several years. Many pathological features of Sjögren's syndrome are similar to those of systemic lupus; perhaps the most interesting is that bodies, remarkably like the hæmotoxyphil bodies of systemic lupus, have been described in the substantia propria of the cornea and sclera in Sjögren's syndrome. I think that Felty's syndrome and Mikulicz's disease, which sometimes occur in association with Sjögren's syndrome, are also forms of systemic lupus, and Dr. F. G. Bolton has found L.E. cells in patients with these conditions referred from the Bristol Eye Hospital.

Systemic lupus is a complex auto-immune disorder, and antibody production is a characteristic feature of the disease. It is therefore not surprising that auto-antibodies have been demonstrated in Sjögren's syndrome.

On the basis of this evidence and much more besides, I have treated about 25 patients with Sjögren's syndrome in the past nine months with antimalarials and have got most encouraging results.

Westbury on Trym, Bristol. J. M. HEATON.

PAPA VIRCHOW

SIR,—It is churlish to denigrate the commemoration of a great man's achievements, but like most of Virchow's good ideas the famous aphorism was not original. It had been used by Raspail in 1825 in the form *omnis cellula e cellula*. Thirty years later, in a polemic editorial entitled Cellular Pathology, Virchow wrote *omnis cellula a cellula* but it did not appear in the *Lectures on Cellular Pathology* until the expanded third edition (1862), when he reverted to Raspail's earlier version.

Virchow's great contribution to the concept of the continuity of cell life was not his originality of thought—indeed many of his own ideas were erroneous—but his propagandist ability to convince his colleagues of the absolute rightness of his views.

Radcliffe Infirmary, Oxford. A. H. T. ROBB-SMITH.

AN OLD NEOLOGISM

SIR,—In your leading article of Sept. 27, entitled Papa Virchow, you describe an early example of a now familiar procedure, the biopsy.

Now that pleas are being made for the adoption of words like " hæmorheology ", it is surprising to find that the well-tried " biopsy " has not yet appeared in our dictionaries on this side of the Atlantic.

The word " biopsie " appears to have been invented by Besnier sometime before the turn of the century. Darier [1] gave its etymology and definition; it is, he said, " *une sorte d' ' autopsie ' sur le vivant* ". The word first entered the dermatological literature, and in its English form can be found in the 1902 volume of the reports of the Dermatology Society of London.[2]

I understand that after more than half a century of hard use the word is to appear in the forthcoming supplement to the Oxford English Dictionary.

Oxford. A. I. SPRIGGS.

1. Darier, J. *in* La Pratique Dermatologique (Besnier, E., Brocq, L., Jacquet, L.); vol. I, p. 472. Paris, 1900.

PSYCHOLOGY OF LABORATORY ANIMALS

SIR,—Dr. Watson (Oct. 4) seems to miss the point. Rats have, of course, been used in innumerable psychological experiments and have provided us with a great deal of information, particularly in regard to motivation and learning. But these experiments have taught us surprisingly little about rats. There is at present a real need for close ethological study of the lower mammals, comparable to that which has already been made with a variety of birds. This might provide important information regarding the social and territorial organisation of rat colonies, both in the wild and in captivity, which would have obvious application to the keeping of laboratory animals. One may therefore warmly welcome UFAW's sponsorship of Dr. Chance's investigation.

The Psychological Laboratory, Cambridge. O. L. ZANGWILL.

PYREXIN AND THE PATHOGENESIS OF FEVER

SIR,—Professor Barry Wood [3] says of pyrexin, the pyrogenic factor extracted in 1943 by me from inflammatory exudates, that " Indeed its resemblance to bacterial pyrogens is so striking that Menkin concludes that pyrexin may be a ' complex ' of bacterial pyrogen with serum-globulin." I have never arrived at such a conclusion, at least as here phrased. The point I made was that bacterial pyrogens when injected intravenously into rabbits convert the euglobulin of blood-serum into a complex pyrogenic factor with biological properties similar in some respects to pyrexin.[4 5] There are, however, striking differences.

For instance, the converted euglobulin of rabbit serum induced by a bacterial pyrogen, injected intravenously into normal rabbits, induced marked fever. On the other hand, the euglobulin fraction of rabbit serum induced by the intravenous injection of pyrexin is wholly inactive.[5] The point of similarity between the bacterial pyrogen " complex " found in the blood and pyrexin is that both are recovered in euglobulin fractions. The bacterial pyrogen " complex " is located in the euglobulin of blood-serum, while pyrexin, on the other hand, is recovered in the euglobulin fraction of primarily acid exudates. There is, therefore, no existing evidence whatsoever for concluding that pyrexin may be a " complex " of bacterial pyrogen with serum-globulin.

Furthermore, the latent period attributed to pyrexin before fever develops is not always long, for a potent pyrexin fraction induces fever in rabbits as early as 15 minutes. In regard to tolerance, I have pointed out that pyrexin *in doses as recovered in exudates* fails to induce tolerance, and that this is the important point in evaluating the role of pyrexin in the pathogenesis of fever with inflammation.[5]

In a recent monograph [6] I expressed the belief that there may well be two factors involved in the pathogenesis of fever—a thermostable one (namely, pyrexin) and a thermolabile one (that described by Bennett and Beeson in 1953 and earlier by Beeson [7] in 1948). I have recently supplied further support for this view, using the method of differential centrifugation.[8] By

2. Fox, C. *Brit. J. Dermatol.* 1902, **14**, 56.
3. *Lancet*, July 12, 1958, p. 53.
4. *Fed. Proc.* 1954, **13**, 439.
5. *J. Lab. clin. Med.* 1955, **46**, 423.
6. Menkin, V. Biochemical Mechanisms in Inflammation. Springfield, Ill. 1956.
7. *J. clin. Invest.* 1948, **27**, 524.
8. *Amer. J. Path.* 1958, **34**, 921.

this procedure two factors, a thermolabile one and a thermostable one (pyrexin), have been identified. The finding of two factors to explain a single biological manifestation of inflammation with its progressive development from an alkaline to an acid pH has already been pointed out.[8,9]

I hope that the foregoing points will supplement the interesting review by Professor Barry Wood.

Temple University School of Medicine, Philadelphia. VALY MENKIN.

REGIONAL HOSPITALS' CONSULTANTS AND SPECIALISTS ASSOCIATION

SIR,—The Royal Commission on the Remuneration of Doctors and Dentists is still sitting and more evidence has to be considered. The findings will probably be published next year, and may be acceptable! This will probably be two years from the time of the inception of the Royal Commission, and the situation is changing. The Joint Working Party on the Medical Staffing Structure in the Hospital Service is now collecting evidence. This inquiry must mainly concern the non-undergraduate hospitals and their staffs. Recently we have heard of the new hospital costing system which has materially increased the charges for private wards, which many of us thought were already too heavy. Many are aware of the delays in making new appointments and appointing successors to retiring consultants in some areas, causing impairment of hospital service and delaying younger men in their promotion.

These are a few of the items which concern the almost inarticulate but greater proportion of the consultants and specialists in Britain.

The Regional Hospitals' Consultants and Specialists Association exists to promote and safeguard the interests of consultants and specialists employed by the regional hospital boards, and as we increase our membership so will our authority and negotiating power be strengthened.

47, Lincoln's Inn Fields, London, W.C.2. HAROLD DODD
President, Regional Hospitals' Consultants and Specialists Association.

HYPERPYREXIA IN ENCEPHALITIS

SIR,—Dr. Johnston and his colleagues (Sept. 27) stated they were unable to find any previous reference to the use of hypothermia in hyperpyrexia of encephalitis. I wish to draw attention to my report of such a case published this year.[10] This patient was treated in St. Laurence's Hospital, Dublin, in May, 1957, and was an encephalitis complicating measles. In comparing the two cases there are a few comments which may be of interest.

The lytic cocktail—namely, chlorpromazine, promethazine, and pethidine—was used for induction and although respirations were noted to be shallow there did not seem to be any further embarrassment during the interval between administration of the cocktail and application of ice; shivering was easily controlled by further doses.

The hyperpyrexia was probably due to cerebral œdema causing hypothalamic pressure. With this in view the patient was controlled at a lower temperature (84–86°F) for a shorter period (16 hours).

We did not experience such a sharp " after rise " of temperature. The temperature rose to 99·5°F which reverted to normal within 3 hours.

Owing to this shorter period, it was found unnecessary to perform a tracheotomy, oxygen bubbled through 'Alevaire' kept the chest clear.

It is possible that hypothermia may be of value in the treatment of other conditions—e.g., hyperpyrexia in fevers whose source is not in the central nervous system, hypertensive encephalopathy in acute nephritis, eclampsia, and tetanus.

Meath Hospital and County Dublin Infirmary, Dublin. GERALD E. EDWARDS.

EXCRETION OF CHOLESTEROL

SIR,—Many reports on atherosclerosis have been concerned with the role of cholesterol, and efforts have been made to correlate high plasma levels of cholesterol with the increase in the total cholesterol of the body arising from the diet or from biosynthesis.[1] In this connection two points are not always made clear: (i) the plasma contains only a proportion of the total sterol of the body and thus plasma levels cannot be the sole guide to metabolic changes involving sterols (cf. work on experimental animals in which livers and other tissues can be examined [2]); (ii) the total quantity of sterol (or indeed of any other component) in the body is the result of a balance between those factors leading to an increase and those leading to a decrease.

A decrease in body cholesterol can occur as a result of transformations or degradations, or by excretion, but until recently very few clinical studies in relation to atherosclerosis have included data on the excretion of cholesterol or its derivatives. It has long been known that lipids, including cholesterol, are excreted through the bowel during fasting, and on fat-free diets, and efforts were made at an early date to ascertain the origin of fæcal lipids. From 1922 onwards, Bloor, Sperry, and their colleagues published a series of reports on the fæcal sterols of experimental animals and came to the conclusion (confirmed in other laboratories) that the sterols were in large part excreted directly through the mucosa of the intestine.

In his review of 1943 Bloor [3] expressed his belief that this work " eliminates the bile as an important path of excretion of the lipids and makes doubtful intestinal bacteria and desquamated epithelium as important sources of fæcal lipids . . . leaving no doubt that there is a considerable true excretion of lipid material ". The Bloor-Sperry conclusions are accepted in various recent reviews,[4–7] and it is therefore perhaps surprising to find that the majority of reports dealing with cholesterol in relation to atherosclerosis ignore completely or refer only cursorily to the question of sterol excretion.

If, however, the results obtained from experimental animals can be applied to man, then the following working hypothesis may be put forward:

(i) Direct excretion of sterol through the intestinal mucosa may be a factor regulating the total sterol content of the tissues.

(ii) Excretion by this channel may depend on the correct functioning of the intestine and normal excretion of sterol may, therefore, depend not only on the supply of dietary essentials for the maintenance of intestinal as well as other body tissues, but also on such well-recognised factors as an adequate amount of roughage in the diet and a minimal amount of bodily activity.

(iii) If the sterol must be in the esterified form to pass through the mucosa, then fatty acids will be required to promote excretion and unsaturated fatty acids (giving more " mobile " cholesterol esters) could have a special significance.

9. Menkin, V. *Schweiz. med. Wschr.* 1952, **46**, 1184.
10. Edwards, G. E. *J. Irish med. Ass.* 1958, **42**, 181.

1. *Nutr. Rev.* 1957, **15**, 282, 309.
2. Deuel, H. J., Alfin-Slater, R. B., Wells, A. F., Kryder, G. D., Aftergood, L. *J. Nutr.* 1955, **55**, 337.
3. Bloor, W. R. Biochemistry of the Fatty Acids and Their Compounds, the Lipids. New York, 1943.
4. West, E. S., Todd, W. R. Textbook of Biochemistry. New York, 1956.
5. Necheles, H., Kirshen, M. M. The Physiologic Basis of Gasto-intestinal Therapy. New York, 1957.
6. Deuel, H. J. The Lipids ; vol. II. New York, 1955.
7. Thannhauser, S. J. *in* Biochemical Disorders in Human Disease. (Edited by R. H. S. Thompson and E. J. King.) London, 1957.

On the basis of this hypothesis excessive plasma-cholesterol levels could arise from the failure of the body to eliminate sterols surplus to normal requirements.

Information regarding the incidence of atherosclerosis in different countries and among different groups in the same country may be correlated with this hypothesis. Two factors may be of importance among prosperous nations and among prosperous sections of the community—namely, the use of diets containing a high content of animal material and/or refined plant foodstuffs with a corresponding decrease in the quantity of roughage; and secondly the decrease in the necessity of physical labour often associated with a marked reduction in physical exercise generally. Both these factors can lead to some degree of constipation (almost unknown among primitive peoples) and, by the hypothesis, a decrease in the ability of the intestine to excrete cholesterol. Other epidemiological studies [8] showing the contrast between urban and rural populations; vegetarian and non-vegetarian groups; peoples of European origin and more primitive races; people in sedentary compared with more active occupations; and between war and post-war years are also consistent with the hypothesis.

There is some recent evidence [9] that the fibre or allied constituents of the diet may exercise some effect on plasma-cholesterol levels and there is older work as well as newer observations, to suggest that certain types of fatty acids may increase fæcal cholesterol levels.[10]

It must be pointed out that Chaikoff and his colleagues,[11] using tracer techniques on experimental animals (and also on one human subject), have demonstrated that the formation of bile acids from cholesterol is a major pathway by which excess sterol is removed from the animal body. Recent reports from South Africa have also indicated the potential importance of bile-acid excretion.[12 13] Nevertheless the tracer studies do not exclude the possibility of other routes of elimination and it is for this reason, and because of the lack of agreement on the role of lipids in relation to atherosclerosis, that attention is now drawn to possible implications of the older work of the Bloor-Sperry school.

Department of Chemistry
and Food Technology,
Borough Polytechnic, London, S.E.1. FRANCIS AYLWARD.

STRANGULATED UMBILICAL HERNIA IN CHILDREN

SIR,—Strangulation of an umbilical hernia in childhood must be very rare: indeed, Mr. Denis Browne [14 15] has been unable to find any record of a case. I therefore report the following:

A West Indian girl had had a soft, reducible umbilical hernia since birth. When 15 months old (on May 8, 1958) she was admitted to Hackney Hospital with a history of severe abdominal pain and a tender umbilical lump for three to four hours, associated with nausea but no vomiting. The hernia was tense and irreducible; its diameter was about 1 in. and it came straight through the centre of the umbilicus, being surrounded by a fibrous collar.

At operation the hernial sac was exposed through a transverse incision, and opened. It contained bloodstained fluid and strangulated gut from the ileocæcal region, purple, and with recent hæmorrhages in the wall of the terminal ileum. After division of the thickened anterior rectus sheath, which was causing constriction, the gut quickly regained its normal colour. The appendix was removed before the gut was returned to the abdomen, and the wound was closed in layers, the rectus sheath being repaired with interrupted, non-absorbable sutures.

Convalescence was uneventful, and the child was discharged a week later.

Hackney Hospital,
London, E.9. R. F. READ.

CONTROL OF THE COMMON COLD

SIR,—The recent observations described by Dr. Ritchie (Sept. 27) and by Dr. Banks (Oct. 4) are to be welcomed as providing further evidence in support of the view that it is the saprophytic bacterial flora of the upper respiratory tract which is responsible for the clinical manifestations of the common cold.

It seems worth restating that dequalinium chloride, a bactericidal chemical agent of wide antibacterial range, appears fully to equal the antibiotics in its therapeutic control of the common cold.[1] Taken in lozenge form, each one containing 0·25 mg. of dequalinium chloride, every two hours on the first day of treatment, and every three to four hours on the following two or three days, also at night time whenever the sufferer happens to awake, it brings, in my experience, an incipient cold to an abortive end and cuts short a fully developed one.

Dequalinium chloride is, of course, free from the disadvantages of antibiotics and its cost is far less.

London, W.1. JOSEPH ZELMANOWITS.

AUSCULTATION OF THE HEART

SIR,—Dr. Leatham (Oct. 11) is to be congratulated on the general excellence of his paper. He mentioned that "Even now some of the existing instruments are of great value in saving time during teaching by permitting large numbers of students to auscultate simultaneously with their own stethoscopes attached to the instrument. The phonocardiogram has also been displayed simultaneously on a cathode-ray tube; but this takes experience to appreciate, and a drawing of the phonocardiogram seems as useful". I take it that this means that the heart sounds are displayed on a single-beam cathode-ray tube, and at the same time the amplified heart sounds are simultaneously auscultated by the students.

A phonocardiogram displayed on the cathode-ray tube, even though accompanied by the amplified heart sounds without a simultaneous interpretative second trace (for instance, an electrocardiogram), is of no great value for teaching purposes. I quite agree that the drawing of the phonocardiogram is about the same value.

However, I am surprised that Dr. Leatham has not mentioned phonoelectrocardioscopy,[2 3] the method described about 15 years ago. The apparatus incorporated a double-beam cathode-ray oscilloscope fitted with a long afterglow screen. It permitted the direct, instantaneous, simultaneous, and constant viewing of a pair of cardiac phenomena, such as the phonocardiogram and electrocardiogram, &c., on the fluorescent screen of the cathode-ray oscilloscope at the patient's bedside without the necessity of photographic registration and consequent loss of time in developing film. The amplified heart sounds were heard while the traces were being directly observed on the screen. The auditory and visual impressions could be simultaneously compared.

Even at this early stage the second interpretative trace was found essential, as it gave visual cues for the interpretation of the phonocardiographic trace. The immediacy of the traces had a dramatic quality compared to the frozen still of the photographic record which was of value in teaching the inexperienced. Phonoelectrocardioscopy also helped in building up conditioned reflexes in the auscultator, as the heart

8. *Lancet*, 1958, i, 625.
9. Walker, A. R. P. *ibid.* 1955, i, 565.
10. Carroll, K. K., Noble, R. L. *Canad. J. Biochem. Physiol.* 1956, **34**, 981.
11. Siperstein, M. D., Chaikoff, I. L. *Fed. Proc.* 1955, **14**, 767.
12. Gordon, H., Lewis, B., Eales, L., Brock, J. F. *Lancet*, 1957, ii, 1299.
13. Lewis, B. *ibid.* 1958, i, 1090.
14. *Brit. med. J.* 1952, ii, 1144.
15. Personal communication, 1958.

1. Zelmanowits, J. *Lancet*, 1958, i, 852.
2. Donovan, G. E. *J. Inst. elec. Engrs*, 1943, **90**, 38.
3. Donovan, G. E. *Lancet*, 1944, i, 500.

sounds were being perceived simultaneously with the phonocardiogram and interpretative trace. The effect of filters could also be immediately observed. Since then I have further developed this method, which is of use in teaching.

West Glamorgan Health Division, Swansea. G. E. DONOVAN.

DOSAGE OF ISONIAZID IN PULMONARY TUBERCULOSIS

SIR,—Workers in the United States, particularly those at this hospital, have for some time been using, in pulmonary tuberculosis, much higher doses of isoniazid than those used in the United Kingdom, Australia, and other countries. This resulted in part from microbiological assay studies showing that isoniazid is inactivated much more rapidly in some patients than in others; and that therefore such patients should receive a much higher dose of isoniazid to maintain an adequate serum level of the biologically active drug. Other workers have also suggested that racial groups may differ in the metabolic inactivation of isoniazid.

It has been found here that patients can tolerate doses as high as 1000–1600 mg. per day with only minor toxic symptoms in a few instances, particularly when combined with pyridoxine 50–100 mg. daily. Russell et al.[1] reviewed a series of 138 cases of cavitating disease treated with combinations of drugs and doses that were considered adequate and appropriate according to blood-level and microbial susceptibility. In only one case did treatment fail.

It is a few years now since the M.R.C. trials were carried out with various combinations of streptomycin, isoniazid, and P.A.S. in pulmonary tuberculosis. Working in chest units in the United Kingdom and Australia, for instance, we adopted the recommendations made by the M.R.C. as a result of those trials, the only difference being that more recently we were using isoniazid doses in the region of 300 mg. daily, and in a few cases up to 400 mg. daily. The best treatment then recommended was daily streptomycin with isoniazid, possibly superseded only by the triple drug therapy, P.A.S. included. Such a combination is still considered the most effective.

It has not been established that the comparatively low isoniazid doses used in the United Kingdom and elsewhere have resulted in more therapeutic failures.[2] But one indeed sees failures of isoniazid when combined with bi-weekly streptomycin, because of the inadequate cover provided by the streptomycin as the second drug. Such treatment is still used today, and drug resistance is common. In the M.R.C. trials this combination was found therapeutically inferior to most of the other drug combinations investigated, and was not recommended.

Accepting the findings of the microbiological assay studies as carried out at this hospital, one can see why the results achieved in Britain and elsewhere were comparable in spite of the lower isoniazid doses used. I have used the records from the department of research and laboratories of this hospital to review the isoniazid blood-level on 550 patients whose ages ranged from 18 to 77. A test dose of 4–8 mg. per kg. body-weight in these patients resulted in a dosage of 200–400 mg. of isoniazid (no P.A.S. was used during this test period). This is comparable to the dose used in the United Kingdom and elsewhere over the past few years. The serum levels of the biologically active drug at six hours after the above loading dosages ranged from 0·4 to 4·8 μg. per ml. in 76·5% of the cases examined. This is considered an "adequate" level for original treatment cases. On the other hand, in 23·5% the level achieved was less than 0·4 μg. per ml.—these are the rapid inactivators of isoniazid.

Studies carried out here, and confirmed by Morse and by Bell, have also shown that P.A.S., by competing with isoniazid for the metabolic inactivation mechanism, raises the actual level of microbiologically active isoniazid. Therefore one could deduce that in this percentage of rapid inactivators the addition of P.A.S. would place many of them in the "adequate" level group. A further study was carried out on 71 cases who achieved an isoniazid level of less than 0·4 μg. per ml. after a dose of 200–400 mg. When P.A.S. (2·5 g. at 0 and 3 hours of the assay studies) was added to the isoniazid, at least two-thirds of the patients achieved an adequate level of the biologically active isoniazid.

Since P.A.S. has been and still is used by many centres in the United Kingdom and elsewhere one can fairly attribute the low incidence of therapeutic failures to the use of P.A.S. with isoniazid. Moreover, many centres also used streptomycin (1 g. per day for a total of 60 to 120 days) in the initial treatment. This again is known to provide an adequate second-drug cover, and therefore the chances of therapeutic failure are even further decreased in the great majority of cases.

In conclusion I must stress the importance of eliminating failures from the initial treatment precisely because of the lack of other comparably active antimicrobial agents. The role of isoniazid dosage becomes important if a low dosage is found directly related to therapeutic failures. On the other hand high isoniazid doses may prove beneficial particularly in centres where ambulatory and domiciliary treatment is carried out on a large scale.

It seems that a controlled study of "low" versus "high" dosage of izoniazid is well indicated in the initial treatment of tuberculosis. The recommended dose of streptomycin is 1 g. or 20 mg. per kg. body-weight per day; and isoniazid could be given in doses of 300 and 900 mg. daily. P.A.S. should be excluded from this therapy because of its established influence on the level of antimicrobially active isoniazid. All other things being equal, the results from such a trial would reflect directly on the dose of isoniazid employed, provided of course that such an investigation included careful drug susceptibility studies.

National Jewish Hospital, Denver, Colorado. ALEX SALIBA.

BLANKETS AND INFECTION

SIR,—With regard to the incidence of cross-infection, our figures (Oct. 4) were based on only a limited number of cases. During the 8 weeks that woollen blankets were employed, one case of cross-infection with *Staphylococcus aureus*, phage-type 80, occurred. There were two cases of cross-infection during the 7 weeks that 'Terylene' blankets were used. No cross-infection occurred over the period of 7 weeks in which cotton blankets were used, although one patient with multiple septic lesions due to *Staph. aureus*, phage-type 80, was present in the ward for 24 days. It will be noted that there were more cases of cross-infection with terylene than with woollen blankets, although the total bacterial air-count was lower with terylene than with woollen blankets. However, reference to table II of our article will show that there was no reduction in the incidence of *Staph. aureus*, phage-type 80, while terylene blankets were used.

In a footnote to our article, we mentioned that untreated woollen blankets, once infected with *Staph. aureus*, retained the viable organisms for 30 days. We have now found that the blankets retain the viable organisms for 8 weeks. However, blankets washed by the 'Lissapol'-

1. Russell, W. F., Jr., Kass, I., Heaton, A. D., Dressler, S. H., Middlebrook, G. Transactions of the 17th Conference on the Chemotherapy of Tuberculosis, 1958; p. 71. Veterans Administration, Washington, D.C., 1958.
2. Crofton, J. *Bull. Un. int. Tuberc.* 1958, **28**, 2.

'Cirrasol' technique, and subsequently inoculated with *Staph. aureus* weekly, retain self-sterilising properties up to 6 weeks after washing. It will be remembered that we were unable to recover viable organisms from cotton blankets on the seventh day after inoculation.

H. SCHWABACHER
A. J. SALSBURY.

Group 9 Laboratory, Watford.

THE A.I.D. INVESTIGATION COUNCIL

SIR,—The Eugenics Society has set up an A.I.D. Investigation Council to consider the present status and future potentialities of artificial insemination by donor—genetic, medical, legal, and social.

The Council has in mind the maintenance of a permanent committee which will at all times have a record of all available data on A.I.D. cases done in this country, with all available medical and scientific information relevant thereto.

The Council would be grateful to hear from any medical practitioner with a contribution to make towards this investigation.

The A.I.D. Investigation Council,
69, Eccleston Square,
London, S.W.1.

PHILIP M. BLOOM
MARGARET HADLEY JACKSON
Honorary Secretaries.

Obituary

JAMES HINTON ROBERTSON

M.B. Glasg., F.R.C.S.E., F.R.F.P.S.

Mr. Hinton Robertson, consulting surgeon to the Victoria Infirmary, Glasgow, died on Sept. 12 at the age of 67.

He was born in Glasgow and educated there at Queen's Park School and the university, graduating M.B. with honours in 1912, and winning the Brunton prize as the most distinguished graduate of his year. After holding resident posts in the Victoria Infirmary he made a sea trip to the East. He joined the French Red Cross early in the 1914–18 war and served in France for about eighteen months. He then returned home, joined the R.A.M.C., and served in the Dardanelles campaign and in East Africa. After he was demobilised he spent four years in general practice at Strichen, Aberdeenshire. In 1924 he was invited to return to Glasgow and join the surgical staff of the Victoria Infirmary. The following year he took the F.R.C.S.E. and the surgical fellowship of the Glasgow Faculty of Physicians and Surgeons, and for the next thirty years he practised as a general surgeon. He was an honorary lecturer in clinical surgery to the university and a past president of the Glasgow Medico-Chirurgical Society and of the Southern Medical Society. For some years he was a member of the board of management of the Glasgow Victoria Hospitals and convener of the medical committee. He retired in 1956.

R. M. writes:

"Hinton Robertson was a most gifted surgeon, sound in judgment, deft and rapid in technique. He was an astute clinical observer, and much of his surgical work showed striking originality of thought and performance. Yet the publication of his results never attracted him, and his writings and addresses always had a historical or philosophical trend. He was widely and deeply read and his conversation was a delight. His great stores of factual knowledge were blended with wisdom and philosophical reflection, and the whole was enhanced by quotation, anecdote, and humorous overtones. Even such a prosaic matter as the reading of a treasurer's report could by the subtle alchemy of his whimsical humour and choice of words be transmuted into an unforgettable performance. He was an excellent public speaker, but he used his gift seldom, and then usually to redress a grievance or to speak on behalf of a younger colleague.

"He was a great clinical teacher of students and the soul of kindness to his juniors, who worshipped him. He was a man of deep religious conviction, and his whole life had something of a saintly quality. Yet there was nothing priggish about him, and no-one was more tolerant towards the weaknesses and shortcomings of his fellow man. No-one had ever heard him utter an angry word even under extreme provocation, though he was a very sensitive man and could be readily hurt. To his colleagues in the hospital he was a tower of strength. They took him all their problems—professional and personal—and they were always sure of enlightenment, balanced judgment, and sympathetic understanding.

"He was very happy in his home life. His recreation was yachting, and up to a few years ago it was his great joy to spend his holidays in the Clyde area and often further afield with his wife and son. About a year ago his health began to fail, but though he was only too conscious of the unfavourable features of his illness, he remained cheerful and active to the end. For this much-loved man St. Paul's words to Timothy are not inappropriate: 'I have fought the good fight. I have finished my course. I have kept the faith.'"

GEORGE FEGLER

M.D. Warsaw

Dr. Fegler, who died in Cambridge on Sept. 23 at the age of 59, had been working for the past seven years at the Agricultural Research Council's Institute of Animal Physiology at Babraham, Cambridge. He came to this country with the Polish Army in 1940 after a research career in physiology which had been interrupted by two world wars.

He was born in the Ukraine of Polish parents, and he first studied medicine at the University of Odessa. He was a prisoner under severe conditions during the 1914–18 war, and he did not return to civilian life until 1922. He completed his medical studies at the University of Warsaw in 1924, and after holding posts in Warsaw and Paris he became professor of experimental pathology at Cracow in 1937. Two years later he was appointed professor of physiology in the University of Vilna, but the late war prevented him from taking up this post and he was attached to a military hospital. With the collapse of Poland he escaped through Rumania to France. He worked for a time for the Polish Army at the Sorbonne and arrived with them in Britain in 1940. In 1941 he became professor of physiology at the Polish School of Medicine in Edinburgh and decided to make Britain his home. He became naturalised and was admitted to the Medical Register. Later his wife and son, who had been separated from him during the war, were able to join him.

After working in the physiology department of the University of Edinburgh on A.R.C. grants he took up his post as principal scientific officer at the institute. Two of his colleagues there write:

"George Fegler's researches were mainly in cardiovascular and respiratory physiology; but during his career many demands were made on his abilities for practical ends, and it was only latterly that he was free to develop his own ideas, which he did with great success. His thermodilution method for measuring blood-flow and cardiac output by the injection of only small quantities of saline has great clinical possibilities as yet unexplored. Despite his interrupted career, with the loss of a chair as soon as he was appointed and grievous personal losses during the war, he never became embittered but kept his quiet, gentle good humour and wit. He was retiring and absorbed in his work, but others were readily infected by his persistent enthusiasm for physiology. The loss of a man of his experience, knowledge, and personal qualities at the height of his powers is a heavy blow to his colleagues and a source of great sadness to his friends."

Dr. Fegler leaves a widow and a son, who has lately graduated in medicine at Edinburgh.

Notes and News

TOOLS OF BIOLOGICAL RESEARCH

REPRESENTATIVES of many different branches of medicine gathered at Guy's Hospital on Oct. 10 for a two-day conference, organised by the department of surgery, on the technical methods of medical research.

In his opening address, Sir Cyril Hinshelwood, P.R.S., emphasised that the essential components of productive research were modern techniques and expert experimental planning. For the research-worker to approach his task effectively he must know which techniques were available and how to use them. That necessitated a breadth of knowledge from which he could select methods suitable for his own problem. Ideas, which were the prelude to new advances, arose by spontaneous eruption from the subconscious mind of the investigator. Therefore, the richer the content of his mind the more likely that ideas would arise. For this reason he should be acquainted with all the principal research weapons in this field of endeavour.

In addition to this general knowledge he should be a master of a specialised technique. This entailed the intelligent use of his technical devices; it was only too easy to be so blinded by technique that no advance in knowledge accrued. To neglect modern methods was to doom oneself to amateurism; if, however, technique became an end in itself it became also a treadmill. Excessive breadth of horizon may lead to dilettantism, but a narrow outlook must result in atrophy of ideas. Unfortunately the very expense of modern apparatus may lead to over-specialisation.

The research team was one way in which specialisation may be achieved without the loss of breadth of knowledge. Collective thought may provide great opportunities for advance, but it had at the same time the risk that a dominant member of the team might create tyranny.

Each must choose for himself in reconciling the extensive on the one hand and the intensive on the other. The good research-worker must have a knowledge of many subjects, but be master of few: he must be a specialist in method but not in mind.

The contributions that followed dealt with the design of experiments (Dr. Peter Armitage), flame photometry (Dr. R. W. R. Baker), electromanometry (Dr. J. P. Shillingford), tissue culture (Dr. Honor B. Fell), tissue transplantation (Dr. L. Brent), electrophoresis (Prof. N. H. Martin), electron microscopy (Dr. J. David Robertson), image intensification (Dr. B. Combee), weighing living cells (Dr. R. Barer), and mass spectrometry (Dr. P. Hugh-Jones). Perhaps one of the most significant comments was made by Dr. Honor Fell, who wondered whether anyone in 1907 could have foreseen that such a highly academic investigation as tissue culture would lead to the very practical poliomyelitis vaccination programme of today.

Sir Eric Riches announced that the papers would shortly be published in book form; and he congratulated Mr. H. J. B. Atkins, the convener of the meeting, on its notable success.

IN SUPPORT OF FACTS

IN its report for 1957 [1] the Nuffield Foundation frankly admits to a "firm, if old-fashioned, belief that if men know the facts of a problem they will usually be able to deal with it better than if they have to depend upon impressions and guesswork". One of our most perplexing and urgent problems today is ourselves, and the Foundation has acted on its old-fashioned belief by allocating much of the £850,000 which it has distributed during the past year to ventures designed to discover facts about human behaviour and relationships.

In 1946 the Foundation started to give priority to biology because it believed that this unfashionable science had important potential contributions to make to medicine and agriculture. During the past year the Foundation held a conference which was attended by a score of biologists under 35, as well as some senior advisers. Their deliberations showed that, though biology can no longer claim help on grounds of neglect, it deserves continuing and expanding support. The following grants, made by the Foundation during the year, indicate the range of their interests in this science:

£34,000 to the department of anatomy, University College, London, to help to build a computer which will resemble the nervous system of an animal. This will be based on Prof. J. Z. Young's studies of the learning mechanism of the octopus and on Dr. W. K. Taylor's small computer which can utter a sound of recognition when a shape resembling one it has learned to classify is put before its electronic eye. It is expected that the new computer will be able to simulate the learning of the alphabet and numerals and a limited number of complex shapes which might even include the human face. The output stage will control levers that will simulate the movements of animals, the production of writing by man, or the generation of recognisable speech sounds.

£1500 a year for two years to the Galton Laboratory, University College, London, for Prof. L. S. Penrose's research into metabolic disturbance in mental defectives, for dietetic experiments with amino-acids in cases of metabolic anomaly, and for clinical trials of biologically active substances.

£3200 to the department of zoology and comparative anatomy, St. Bartholomew's Hospital, London, towards Dr. A. J. Marshall's study of the effects of radioactive fallout on wild animal population. Birds which normally arrive in Africa in winter plumage are reported to have already assumed their summer plumage. Migratory plovers and redshanks coming to winter in Britain have also changed their plumage unseasonably, and some of these have been found to be radioactive. Dr. Marshall is to collect freshwater fish, amphibians, reptiles, birds, and mammals in different parts of Australia and in areas where there has been intense exposure to fallout.

£1750 for capital expenditure and £9250 over three years to Dr. D. R. Newth to set up a research unit in the department of zoology, University College, London, to investigate whether it is possible to provoke in the cells of higher animals the kind of genetic change known as transformation in bacteria.

£6500 over three years to the department of bacteriology, Royal Veterinary College, London, for research into calf diarrhœa. Prof. R. Lovell believes that the relation between *Escherichia coli* infections in domesticated animals and in infants can usefully be studied from this angle.

The Foundation has always set aside part of its resources to help work in Commonwealth countries. It is especially anxious to sponsor projects which may help to advance the well-being of their communities. Two well-chosen grants of this kind are:

£20,000 to the Central Medical School, Fiji, where Dr. Roy Edmonds, the principal, plans to set up a department to teach techniques of preventive medicine to ancillary workers as well as medical students and to carry out research into the effect of changing conditions on the population of the islands.

A further grant of £10,000 to the experimental rural hospital and health centre near the Christian Medical College, Vellore, where students are shown the conditions they are likely to meet in practice in country districts. The project has proved so successful that the University of Madras is adopting a similar scheme in its medical college.

1. Nuffield Foundation report for the year ended March 31, 1958. Obtainable from Nuffield Lodge, Regent's Park, London, N.W.1.

University of London

At recent examinations the following were successful:

D.P.H.—Louis Baldacci, Jahar Lal Bose, J. M. Davies, R. O. M. Jones.

University of Bristol

On Tuesday, Oct. 28, at 8.15 P.M., at the H. H. Wills Physics Laboratory, Royal Fort, Prof. A. I. Darling will give the Long Fox lecture on decay of the teeth. On Thursday, Nov. 20, at 8.15 P.M., at the university, Dr. Bernard Schlesinger will give the Carey Coombs lecture on the course and treatment of rheumatoid diseases in childhood. Tickets for this lecture may be had from the registrar, The University, Bristol, 8.

Faculty of Radiologists

A postgraduate course will be held at the Royal College of Surgeons on Saturday afternoon and Sunday morning, Nov. 22 and 23. Particulars may be had from the Faculty's office at 47, Lincoln's Inn Fields, London, W.C.2. Enrolments and the fee of 16*s*. must be received by Nov. 15.

Royal College of Surgeons of England

AT a meeting of the council on Oct. 9, with Sir James Paterson Ross, the president, in the chair, Mr. W. A. Mill was admitted to the court of examiners.

The Mitchiner medal was presented to Lieut.-colonel R. H. Robinson, and the Handcock prize to Mrs. E. M. Cooke (Royal Free School of Medicine). The John Hunter medal and triennial prize were awarded to Dr. L. W. Proger for his services to the Hunterian museum. A Mackenzie Mackinnon research fellowship was awarded to Mr. K. E. D. Shuttleworth.

Diplomas were granted to the following:

F.R.C.S.—B. P. Scrivener.

F.F.A. R.C.S.—Jean M. Horton, S. W. Kemp, B. R. J. Simpson, J. D. K. Burton, T. M. McAneny, A. McL. Keil, Patricia Painter, R. L. Hargrove, T. M. Ness, Sivasubramaniam Thirumalai, J. L. Hadley, Ellen R. Armitage, A. J. Booth, Sheila R. Clarke, B. J. Muir, J. R. Munro, Basil Solomon, F. Rajendram Bhupalan, F. S. Keddie, R. M. Nicholl, T. J. Stanton, George Tay, H. R. P. Coutanceau, G. W. Duckworth, G. L. F. Lau, Prabhakar Mayabhai Mehta, I. A. Sloan J. V. Farman.

M.R.C.S.—A. B. Richards.

The following diplomas were granted jointly with the Royal College of Physicians:

D.I.H.—M. C. Gupta.

D.P.H.—D. S. Jani

D.P.M.—G. Woolfson.

D.A.—D. M. Davies.

D.O.—Amiya Kumar Banerjee J. Chiaonan Chang, Kai Kai Chau, Sudhir Ranjan Chowdhuri, B. P. Cooper, R. J. Croke, Elizabeth L. R. Douglas, Lal Krishna Dutta, J. M. Elsby, Asuncion N. Fernando, Raghubir Singh Garkal, J. H. L. George, Pratip Kumar Ghosh, Elizabeth F. Hamilton, A. C. A. Hempel, D. E. Hone, Mohammed Ismail Khan, Salam Khoshnevis, Avadhani Krishna Murthy, Percy Lancer, M. G. Lyall, A. J. Lyne, Alfred Lytton, Krishnalal Jivanlal Modi, Venkatesh Shridhar Pande, Madanmohan Vithaldas Parikh, J. A. Pearce, H. J. Penkala, Pe Than Maung, Dara Naservanjee Randeria, J. M. Rodd, P. G. Rowsell, Indra Shekher Roy, Moti Lal Sharma, Sardar Ali Sheikh, G. E. M. Smith, Gian Chand Sood, D. J. Thornton, N. H. Welsh, G. S. Willetts, M. S. Wilson.

D.C.H.—Vijai Krishna Agarwal, Vijay Chandra Agarwal, Hilary Allin, Elizabeth M. F. Andrews, K. D. Austin, J. F. Baden-Daintree, Sankhadhar Barua, Nagalingam Bhaktilingam, Josephine Bradford, Helen R. L. Brown, K. W. Browne, Anne J. Burge, Mary S. Campbell, Jitendra Chandra Chakrabarti, Chin Por Chin, Devinder Raj Chopra, Ram Karan Chopra, Joseph Connolly, M. J. Conway, Izette R. Coulton, P. N. Cretney, Edith Danos, B. S. David, Govind Narayan Dubey, Victor Dubowitz, F. M. Elderkin, J. H. Fairley, Hazel M. Fearn, W. R. Forbes, R. A. Gould, Margaret S. Hall, Jean G. Harrison, Iqbal Ahmed Hashimi, Anne Heath, C. P. Hindley, Barbara L. Hooker, M. J. Howell, David Hull, Rosemary Hulley, J. A. Inall, Sarojini Isaac, Wilma J. Israelsohn, Celia A. James, G. W. Johnston, John Keane, Katie Keane, Pandramajal Narayanappa Krishnamurthy, Julie Sian Sek Lim, H. M. Lipman, Gwendolen Mallal, A. V. Mar, Valerie J. Marrian, W. C. Marshall, A. P. Mayne, Gopal Krishna Mehrotra, Hamida Sultana Memon, A. K. Miller, Avinash Mithal, D. M. Morgan, Khursheed Moulvi, Janice H. Mount, J. E. Newcombe, Heather B. Nunnerley, Susan B. Gyankoramah Ofori-Atta, J. P. O'Neill, Mehroo Savaska Pardiwalla, Kantibhai Maganbhai Patel, Peter Pitney, Norah T. E. Power, H. V. Price, Ann Priestman, Gillian Prosser-Ashby, Kulsum Abdulla Rahimtulla, Shirley G. Ratcliffe, Leonard Sash, Ronald Schofield, Shamim Shabbir, Jean Shackleton, A. J. H. Shepherd, Kamal Soni, Anne L. Stewart, Susan Stonestreet, M. K. Strelling, Margaret J. D. Sturges, Hui Lim Helen Tay, A. F. Taylor, Dileas M. Tingle, Hessel Lionel Utian, Noor Ali Vellani, Geraldine M. Walshe, Keith Warburton, R. W. Watton, Mary Wilkie, Raymond Winstone, Lina Yut Lin Yong.

D.T.M. & H.—Shamsul Abedin, Aladdin Abdul Aziz Ahmed, Kamla Bery, F. S. Boi-Doku, M. C. Brain, K. R. Bremner, D. G. Carlson, Hin-Wing Chan, D. P. Daly, M. E. Fearnley, R. D. Foord, Dhananjay Amthalal Gandhi, D. J. Hansman, Thein Htun, H. Ariarathinam Jesuthasan, Bishwambhar Jha, Hassan Ali Fazal Virani Kassam, Hoshang Jal Khambatta, Mohamad Ataullah Khan, Monawar Din Khan, Kewku Kyir Korsah, M. C. Latham, P. B. Lees, Mahmoud Hussein Mahmoud, Kamal Kumar Mallik, Mohammed Abdul Mannan, F. X. Martin, Mookencherry Cherian Mathews, R. A. Miller, Damodar Misra, M. T. Moore, Hossein Nadjy, Rosemary A. Page, G. M. J. Pais, Valerie J. Prior, Sharafat Husain Qureshi, W. H. Rees, Surendra Pranlal Shah, Jagannath Sharan, Ramanuj Prasad Singh, Ramji Singh, Dankmar Raphael Stein, Bangalore Venkataramiah Suryanarayana, Nyamatmiyan Akbarmiyan Syed, Ibrahim Taha, Tha Khin, Thavorn Thavornsiri, Ernest Trinick, K. E. Ussher, Noor Ali Vellani, Cyrus Vesuna, A. E. Wanigesooria, Anje Wiersinga, Muhammad Hayat Zafar.

D. Phys. Med.—E. N. Coomes, Robert Danbury, Helene V. Goodman, George Holden, K. H. Nixon, Sanat Kumar Sarkar, V. L. Steinberg, W. G. Wenley, V. B. Whittaker.

Royal College of Obstetricians and Gynæcologists

On Friday, Nov. 7, at 4 P.M., at the college, 58, Queen Anne Street, London, W.1, Mr. J. M. Crawford will give a William Blair-Bell lecture on placental growth in normal pregnancy and in erythroblastosis fœtalis.

Uses of Plastics in Medicine

A course of six lectures on this subject will be given on Wednesdays from Oct. 29 to Dec. 3, at 6.30 P.M. at the National College of Rubber Technology, Northern Polytechnic, Holloway Road, London, N.7. The speakers will include Dr. J. T. Scales, Prof. C. G. Rob, and Dr. S. A. Leader. Further particulars may be had from the head of the college.

Association of Clinical Biochemists

The following officers have been elected for 1958–59:

President, Prof. E. J. King; chairman, Dr. A. L. Latner; hon. treasurer, Dr. J. H. Wilkinson; hon. secretary, Dr. A. L. Tárnoky, Royal Berkshire Hospital, Reading.

Ophthalmological Society of the United Kingdom

The annual congress of this society will be held at 1, Wimpole Street, London, W.1, from April 9 to 11. Further particulars may be had from the hon. secretary of the congress, Mr. E. C. Glover, 47, Lincoln's Inn Fields, W.C.2.

Research Defence Society

On Tuesday, Nov. 18, at 5.30 P.M., at the Zoological Society of London, Regent's Park, N.W.1, Mr. Richard Fort, M.P., will give the Stephen Paget lecture. His subject will be The Irrational in Public Life.

Royal Institute of Public Health and Hygiene

On Tuesday, Nov. 11, at 4 P.M. at the institute, 28, Portland Place, London, W.1, Brigadier Sir John Boyd will give the Blackham lecture on yellow fever and its prevention.

Congress of the European Society of Hæmatology

This congress will be held in London from Sept. 7 to 12, 1959. Further particulars may be had from Dr. E. Neumark, department of pathology, St. Mary's Hospital, London, W.2.

Anglo-French Exchange Bursaries

Applications are invited for bursaries to be awarded in 1959 to young British doctors under the exchange scheme arranged by the French Embassy in London between the Institut National d'Hygiène in Paris and the Ciba Foundation in London.

The grants (60,000 francs a month) will be awarded for two to four months to medical men who wish to obtain clinical experience or carry out research in France. Application forms may be had from Dr. G. E. W. Wolstenholme, director of the Foundation, 41, Portland Place, London, W.1. The closing date for applications is Jan. 31, 1959.

London Hospital Dinner

At the old students' dinner on Oct. 9, Dr. H. B. May, the dean, spoke of the rebuilding of the hospital.

The first phase—the rebuilding of the bombed block—had already started: spread over five years, it would cost £500,000–£600,000, largely from free funds. Within the next year or eighteen months the students' hostel would be completed, as a quadrangle of which the exsiting building would form not more than half. Funds for this (about £100,000) would be provided by London University.

Sir Russell Brain proposed The Chairman, Dr. A. E. Clark-Kennedy.

"C. K.", he said, had changed little in the 40 years they had known each other, and the cross-country runner of those days had (until recently at least) continued to run a mile in the hospital sports—disappointing the students who waited with a stretcher. In the old days he had hunted foxes on foot in the lanes but now he rode to hounds. Then he was writing the life of Stephen Hales, and now he was still writing. His highly individual textbook of medicine had been followed by a new art form—the medical novel. He had been a great dean, and he was a great teacher because he was a great doctor. He fulfilled the hospital motto in that "there is nothing in the human situation which he does not find of interest and concern".

Dr. Clark-Kennedy, in reply, spoke of the advantages of serving two masters: his duties at Corpus Christi College, Cambridge, always gave him an alibi when there was work in London, and vice versa. And when, despite this, there was more work than he liked, it was done by Mr. Burden and Mr. Osman—"those two great servants of the medical school". Human happiness, he felt, depends on developing and maintaining a right pattern of loyalties, and the increasing size of the hospital made it necessary to hold like grim death to the things that are worth while. The risk was that the medical school, instead of being an integral part of the hospital, would become a teaching machine loosely superimposed on a hospital run by a board of governors for the Minsitry of Health. He appealed to old Londoners to stick together, and to the hospital staff, though now so much more numerous, to show continually, as in the old days, their interest in the school.

International Congress on Plastic Surgery

The British Association of Plastic Surgeons is holding a congress in London from July 12 to 17, 1959. Further particulars may be had from the organising secretary, Mr. David Matthews, Institute of Child Health, Hospital for Sick Children, Great Ormond Street, London, W.C.1.

Meeting of Endocrinology Societies

A meeting sponsored by the section of endocrinology of the Royal Society of Medicine and the Society for Endocrinology, with the participation of the Society for the Study of Fertility, the medical section of the British Diabetic Association, the London Thyroid Club, and the Endocrine Club, Glasgow, will be held on April 24 and 25 at the Royal Society of Medicine. Further particulars may be had from the hon. secretary of the section of endocrinology, Royal Society of Medicine, 1, Wimpole Street, London, W.1.

Dr. P. M. F. Bishop will give a series of lecture-demonstrations in endocrinology at Guy's Hospital, London, S.E.1, at 5.15 P.M. on Mondays from Oct. 20 to Dec. 15.

The dinner of the Society of Medical Officers of Health will be held at the Royal College of Surgeons, Lincoln's Inn Fields, London, W.C.2, on Thursday, Oct. 23. Dr. J. A. Stirling will be in the chair and Mr. Derek Walker-Smith, the Minister of Health, will propose the toast of The Society.

The annual dinner of the Glasgow University Club, London, will be held at the Trocadero Restaurant, London, W.1, at 7.30 P.M. on Thursday, Nov. 6. Further particulars may be had from Dr. J. F. Heggie, department of pathology, North Middlesex Hospital, Edmonton, N.18.

The autumn dinner of the Wessex Rahere Club will be held on Saturday, Nov. 1, at the Grand Spa Hotel, Clifton, Bristol. Further particulars may be had from the hon. secretary, Mr. A. D. Bateman, 11, The Circus, Bath, Somerset.

The proceedings of the symposium on the Teaching of Sexual and Marital Relations to Medical Students, held by the British Medical Students' Association in Cardiff last year (*Lancet*, 1957, ii, 1112), may be had from the B.M.S.A., B.M.A. House, Tavistock Square, London, W.C.1.

Appointments

BLENKINSOP, E. I., M.B. Durh., D.P.H.: deputy M.O.H. and deputy principal school M.O., Dewsbury.
ROBERTSON, M. C., M.B. Leeds: assistant M.O., Brigg and Barton area of Lindsey.
SEYMOUR, FRANCIS, M.B. Lpool, D.P.H.: M.O.H., Amersham, Beaconsfield, and Chesham, and deputy divisional school M.O. and assistant M.O., Buckinghamshire.
WEBB, B. W., M.D. Lond., M.R.C.P., D.C.H.: consultant pædiatrician, South Somerset clinical area.
WILSON, HAZEL M., M.R.C.S.: registrar in mental deficiency and child psychiatry, Little Plumstead mental deficiency group of hospitals and child psychiatry service.

The Hospital for Sick Children, Great Ormond Street, London:

BIRCH, DOREEN A., M.B. Cape Town, F.R.C.S.: registrar, E.N.T. department.
GUTHRIE, E. J., M.B. W'srand: house-surgeon, orthopædic and plastic departments.
KENNEDY, W. P., M.D. McGill, D.C.H.: assistant medical registrar.
MACKENZIE, Y. D., M.D. Lond., M.R.C.P.: registrar, department of physical medicine.
MILES, MARION V., M.R.C.S., D.C.H.: house physician.
STURDY, D. E., M.B. Lond., F.R.C.S.: surgical registrar.
VAN WATERSCHOODT, ALICE E. M., M.B. Lond., D.OBST., D.A.: junior anæsthetic registrar.

Liverpool Regional Hospital Board:

CUTHILL, I. M., M.B. Edin., M.R.C.P.E.: assistant chest physician, Chester and district area hospitals.
OGILVIE, C. M., M.D. Lpool, M.R.C.P.: part-time consultant physician, regional thoracic surgery unit, Broadgreen Hospital.
O'NEILL, P. B., M.B. Lond., F.R.C.S., D.L.O.: part-time consultant oto-rhinolaryngologist, St. Helens, Warrington, Ormskirk, and Runcorn area hospitals.
OWEN, W. M., M.B. Lond., F.R.C.S., D.L.O.: part-time consultant oto-rhinolaryngologist, Clatterbridge and Wirral Hospitals.
PARRY, H. E., M.B. Lond., M.R.C.P., D.C.H.: consultant physician and deputy medical superintendent, Fazakerley Hospital.
SIEGLER, JOSEPH, M.B. Lond., F.R.C.S., D.L.O.: part-time assistant consultant otorhinolaryngologist, Bootle, Walton, and John Bagot Hospitals.
WALKER, ERIC, M.D. Lpool, D.M.R.D., D.P.H.: part-time consultant radiologist, Sefton General Hospital.
WILSON, J. K., M.D. Lpool, M.R.C.O.G.: part-time consultant obstetrician and gynæcologist, Ormskirk County Hospital.
WOODCOCK, A. S., M.D. Leeds, consultant pathologist, Whiston and Rainhill Hospitals.

Diary of the Week

OCT. 19 TO 25

Sunday, 19th

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
10.15 A.M. Mr. Anthony Radcliffe: Common E.N.T. Conditions.

Monday, 20th

UNIVERSITY COLLEGE LONDON, Gower Street, W.C.1
5.30 P.M. Dr. E. Gutmann (Prague): Nervous Regulation of the So-called "Trophic Processes" in Striated Muscle.

HUNTERIAN SOCIETY
8.30 P.M. (Talbot Restaurant, London Wall, E.C.2.) Dr. Francis Leslie: Thirty Years' Experience in General Practice. (Presidential address.)

Tuesday, 21st

BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1.) Prof. C. H. Stuart-Harris: Adenoviruses and Respiratory Disease in Man.

ST. MARY'S HOSPITAL MEDICAL SCHOOL, Paddington, W.2
5 P.M. Dr. Shila Ransom: Analgesic Drugs Used in Labour.

INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. J. S. Pegum: Hair Growth.

SOCIETY FOR THE STUDY OF ADDICTION
8 P.M. (11, Chandos Street, W.1.) Prof. A. D. MacDonald: Use and Abuse of Tranquillisers.

UNIVERSITY OF LIVERPOOL
5.15 P.M. (New Medical School, Ashton Street, Liverpool.) Mr. R. C. J. Hill (Durban): Tuberculosis in the Bantu.

Wednesday, 22nd

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
5 P.M. *Endocrinology*. Prof. F. T. G. Prunty: Interpretation of Hormonal Abnormalities. (Presidential address.)

SOCIETY OF BRITISH NEUROLOGICAL SURGEONS
5.30 P.M. (London Hospital, Whitechapel, E.1.) Sir Geoffrey Jefferson: Hugh Cairns. (First Hugh Cairns lecture.)

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.12
2 P.M. Prof. C. H. Gray: Role of the Endocrine Organs in Diabetes Mellitus.

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. Henry Haber: Benign Skin Tumours of Ectodermal Origin.

INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Dr. J. R. May: The Place of *H. influenzæ* in Chronic Respiratory Infections.

INSTITUTE OF OBSTETRICS AND GYNÆCOLOGY
4.30 P.M. (Chelsea Hospital for Women, Dovehouse Street, S.W.3.) Prof. H. C. McLaren: Diagnosis and Treatment of Carcinoma in Situ.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE, 28, Portland Place, W.1
3.30 P.M. Surgeon Rear-Admiral S. G. Rainsford: Ionising Radiations in Industry—The Medical Problem.

MANCHESTER MEDICAL SOCIETY
5 P.M. (Medical School, University of Manchester.) Dr. F. R. Ferguson: Neurology—Bridging the Gap. (Presidential address.)

UNIVERSITY OF LIVERPOOL
5.15 P.M. (New Medical School.) Sir Ronald Fisher: Smoking and Cancer.

Thursday, 23rd

BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine.) Dr. D. G. Evans: Vaccination Against Poliomyelitis.

ROYAL SOCIETY OF MEDICINE
8 P.M. *Urology*. Mr. A. W. Badenoch: Injuries of the Ureter. (Presidential address.)

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. J. O. Oliver: Sebaceous Glandular System.

Friday, 24th

ROYAL SOCIETY OF MEDICINE
5 P.M. *Pædiatrics*. Dr. Aubrey Leatham, Dr. Geoffrey Dawes, Dr. Eric Burnard, Dr. R. E. Bonham-Carter: Significance of Cardiac Murmurs in the First Few Days of Life.

POSTGRADUATE MEDICAL SCHOOL
10 A.M. Mr. F. B. Cockett: Surgery of Venous Ulceration of the Leg.
4 P.M. Dr. D. A. K. Black: Renal Circulation.

INSTITUTE OF OBSTETRICS AND GYNÆCOLOGY
4.30 P.M. (Queen Charlotte's Hospital, Goldhawk Road, W.6.) Prof. W. I. C. Morris: Mechanism of Blood Coagulation and its Obstetric Disorders.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY
5.30 P.M. Prof. C. V. Harrison: Pathology of Malignant Lymphomas.

Saturday, 25th

FACULTY OF RADIOLOGISTS
10.30 A.M. (University of Sheffield.) Mr. F. W. Holdsworth, Prof. D. H. Collins, Dr. L. L. Ralph, Dr. J. Walter: Primary Tumours of Bone.
2.15 P.M. Meetings of diagnosis and radiotherapy sections.

CORRIGENDUM: *Oral Treatment of Pernicious Anæmia*.—In the letter by Dr. Herbert and his colleagues last week (p. 801) a sentence began "11 consecutive patients in one study [4] . . ." This study is in fact that recorded in footnote 2 (Estren, S., Wasserman, L. R. *Proc. Soc. exp. Biol., N.Y.* 1956, **91**, 499).